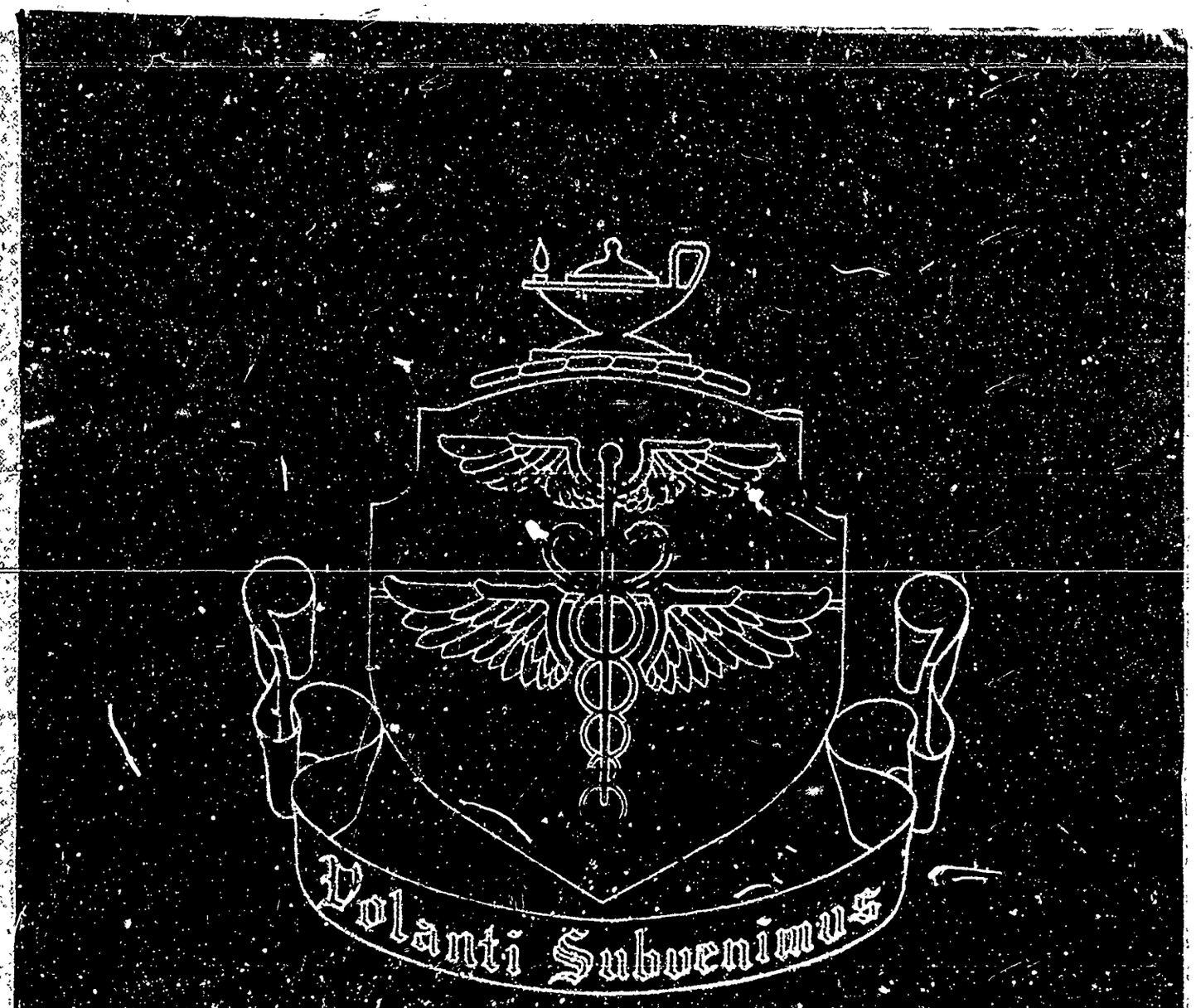

ACCLIMATIZATION VERSUS TOLERANCE TO STRESS

An Annotated Bibliography

Volume II

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FOREWORD

This bibliography was compiled by members of the Life Sciences Department, Space and Information Systems Division, North American Aviation, Incorporated, Downey, Calif., under task No. 793002 and contract No. AF 41(609)-2335. The program was begun in May 1964 and completed in July 1965. The work was monitored by personnel in the Environmental Systems Branch, USAF School of Aerospace Medicine. The material was submitted for publication on 20 July 1967.

This is the second of two volumes. Section I, "Acclimatization and Chronic Hypoxia," made up the first volume.

This report has been reviewed and is approved.

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ABSTRACT

This volume is a continuation of the literature survey conducted to evaluate acclimatization versus tolerance to stress and contains a compilation of titles and abstracts dealing with altitude acclimatization as related to acute hypoxia, decompression, hypercapnia and hyperthermia. The bibliography is arranged alphabetically by authors' names.

CONTENTS

INTRODUCTION

The physiological desirability of the composition of a space cabin atmosphere is usually assumed to bear a direct relationship to the closeness with which the given atmosphere approximates the earth's sea-level atmosphere. Deviations from this thesis have included suggestions of hypothermia for the reduction of metabolic rate, the substitution of other inert gases for nitrogen to reduce the potential for the bends, and finally an atmosphere equivalent to one which produces altitude acclimatization in mountain dwellers. This last consideration is of interest here.

From the early work of Mosso, Bert, Muller, Barcroft, Haldane, to the more recent work of Hurtado, Chiodi, Merino, Kellog, Dill, etc., evidence has accumulated to show that the body, through various physiological adaptations, produced over a period of time, is capable of carrying out normal activities at altitudes from 12,000 to 18,000 feet. Previously acclimatized crewmen operating in a cabin atmosphere equivalent to 12,000 to 15,000 feet of altitude should, therefore, show no decrement in normal performance. Of primary interest is the comparison between the tolerance of the acclimatized crewman to various other stresses imposed by the mission, either accidental or anticipated, and the tolerance of the unacclimatized crewman operating in a normal oxygen environment.

Stresses such as acute hypoxia, hypercapnia, decompression, hyperthermia, acceleration, and exercise could be expected to occur most commonly during space flight.

Experimental evidence indicates that acclimatization to altitude significantly increases tolerance to acute hypoxia and to decompression. The other stresses have not been thoroughly investigated. The purpose of the present study is to establish a relationship between the physiological changes of altitude acclimatization and tolerance to the above-listed stresses.

Preliminary to the formulation of an experimental program, attempts have been made to establish theoretical relationships between physiological changes of altitude acclimatization, changes produced by acute exposure to each stress, and changes produced by a prolonged exposure to each stress. The literature which was utilized in the establishment of these relationships is presented here in the form of an annotated bibliography.

II. ACUTE HYPOXIA

A

Abramson, D. I., H. Lanot, and J. E. Benjamin. Peripheral vascular response to acute anoxia, Arch. Intern. Med. 71:583 (1953).

Adolph, E. F., and P. A. Hoy. Postnatal development of diuresis in response to postnatal hypoxia. Red. Proc 14 (1^{i}): (2 Mar. 1955). Exposure to an atmosphere with an oxygen partial pressure of 42 to 46 mm. Hg resulted within 2 minutes in anuria or oliguria in infant rats. Diuresis occurred 15 to 30 minutes after return to a normal atmosphere. Since the diuretic response to hypoxia was greater at five days of age than at two days of age, its development was seen to be postnatal.

Agostini, A. Alternating repolarization. Folia Cardiol. (Milan) 14(2):97-106 (30 Apr. 1955) Electrocardiographic changes of the ST segment and the T wave were observed in two dogs rendered anoxic by breathing a mixture containing 7-percent oxygen in nitrogen. The same phenomenon was noted following the intravenous administration of pitressin (vasopressin). This change in the ST segment and T wave was a reversible phenomenon and could be

reproduced many times in the same animal following the successive administration of pitressin. The phenomenon is often limited to a relatively circumscribed zone of the ventricle, most frequently in the region of the cardiac apex. A brief note is presented on the possible origins of the phenomenon, and the hypothesis is proposed that the change in repolarization is due to subendocardial insufficiency.

Altland, P. D., B. Highman, and J. Roshe. Effects of altitude on dogs with valvular heart disease: tolerance and pathologic effects of acute and chronic exposures. A. M. A. Arch. Path. 68:475-486 (Nov. 1956).

Altland, P. D., and B. Highman. Effect of repeated acute exposures on longevity in rats. Amer. J. Physiol. 168:345-351 (Feb. 1952).

Arnould, P., and M. Lamarchi. Modifications of the blood mass and the interstitial fluids during acute anoxia in the chloralosed dog. Med. Aero. (Paris) 7(4):522-528 (1952). Chloralosed dogs were subjected to acute anoxia by breathing a mixture of 10-percent oxygen and 90-percent nitrogen. During anoxia, part of the blood

plasma passed to the interstitial spaces and thus produced an increased hemoconcentration, but the total volume of extracellular fluid remained unchanged; the total blood cell volume remained constant. Oxyhemoglobin saturation was reduced from a normal 94.4 to 69.6 percent.

Asmussen, E., and H. Chiodi. Effect of hypoxemia on ventilation and circulation in man. Amer. J. Physiol. 132:426-436 (1941).

Astrom, A. Opinions on rescue from high altitudes. Meddelanden fran Flygoch Navalmedicinska Namden (Stockholm) 4(3):18-21. (1955). The author discusses aeromedical problems arising from rapid drops in atmospheric pressure, i.e. during ascent and flight at altitude (15,000 to 20,000 meter). The primary effects include mechanical effects on the lungs, expansion of gas volume (enclosed in sinuses, middle ear, and intestines), gas bubble formation (causing bends, chokes, etc.). Overpressure equipment, i.e., vest, antigravity suits, capstan suits, full pressure suits) are outlined. Equipment designed to protect the pilot after explosive decompression should feature automatic actuating devices due to

the short time span of 11 to 15 seconds between decompression and black-out. A diagram shows variations in pulmonary gas pressure between 0 - to 20,000- meter altitude during air breathing and during 100 percent oxygen respiration. The following protective equipment design requirements for ejection at high altitudes are discussed; catapult equipment, face protection, tumbling after ejection, low temperatures at high altitude and on the ground, and pressure differential between the cockpit and the outside.

Aviado, D. M., J. Ling, and C. Schmidt. Effects of anoxia on pulmonary circulation: reflex pulmonary vasoconstriction. Amer. J Physiol. 189(2):253-262 (May 1957). Anoxia in dogs caused by exposure to 5- or 10-percent oxygen produces increased pulmonary arterial pressure and blood flow but variable pulmonary vascular resistance. Four factors effect pulmonary vascular resistance; reflex pulmonary vasoconstriction, local pulmonary vasodilation, passive reduction in pulmonary vascular resistance, and release of epinephrine capable of stimulating the heart and constricting the lung vessels. The reflex pulmonary

vasoconstriction is mediated by the thoracic sympathetics and is activated by less severe anoxemia (reduction of arterial O_2 saturation by at least 10 percent) as compared to the other mechanisms, i.e., local and passive dilatation which require reduction of saturation of at least 30 percent.

Aviado, D. M., et al. Effects of anoxia on pressure, resistance, and blood (P^{32}) volume of pulmonary vessels. Amer. J. Physiol. 169(2):460-470 (1952). The factors interacting in the regulation of the pulmonary circulation under conditions of anoxia (5- to 10-percent oxygen) were studied in dogs. Anoxia produced a rise in pulmonary arterial pressure which can be explained as the result of the increased pulmonary blood flow brought about by carotid and aortic chemo-reflexes through the liberation of epinephrine. Dilatation of pulmonary vessels can be seen when the lung is perfused with oxygen-deficient blood. During anoxia there is an increase (demonstrated by P^{32}) in the blood content of the lung.

Balke, G. Human tolerance. In Brown, J. H. U. (ed). Physiology of man in space, pp. 149-171. New York and London: Academic Press, 1963. This study covers the tolerance of the "average" individual for various space flight stresses. It is presumed that the subject has used all potential training and conditioning facilities for achieving the maximum level of adaption for psychophysiological stresses, including: gravitational forces (acceleration, deceleration, and weightlessness), hyperventilation, high altitude (pressure suit, normal air breathing, 100 percent oxygen, and oxygen under pressure), dysbarism (decompression sickness), hypercapnia, temperature extremes, and physical work (functional limitations, metabolic limitations, and environmental effects on work capacity).

Barer, A. S., and E. V. Iakaleva. Changes in the concentration of sodium and potassium ions in the human urine and saliva during "ascents" in a barochamber to 5000 and 6000-meter altitudes. Buill. Ysk. Biol. Med. 53(1):63-65 (Jan. 1962). Salivary and urinary sodium and potassium concentrations were studied by flame

photometry in 26 and 24 subjects at simulated altitudes of 5000 (30 minutes) and 6000 meters (15 minutes) respectively. Samples of urine and saliva were obtained before, during, and after the stay in the barochamber. Regular shifts were seen in the Na and K concentration and the Na/K ratio. The concentration of K-ions had a tendency to rise, while that of Na dropped. With repeated ascents the shifts became smoother.

Barker, J. N. Role of hemoglobin affinity and concentration in determining hypoxic tolerance during infancy, hypoxia, hyperoxia, and irradiation. Amer. J. Physiol. (1957).

Bartlett, R. G., and R. A. Hectz. "Subclinical" respiratory disease and altitude tolerance in the rat. Aerospace Med. 34(1): 18-20 (Jan. 1963). Rats with "subclinical" respiratory disease (pneumonia) were exposed to a simulated altitude of 33,500 feet with appropriate controls. Altitude tolerance, as indicated by survival at altitude, was significantly less in "sick" animals than in controls.

Bassi, M., and A. Bernelli. Preliminary studies on the metabolism of vacuolated cells following hypoxia. Experientia (Basel) 11(3):105-106 (1955). Vacuolated liver cells were produced in adult albino rats by exposing the animals to an atmosphere of 97-percent nitrogen and 3-percent oxygen for 2 hours. Analysis of liver slices indicated that the respiratory quotient, labile phosphorus, and total high energy phosphate bonds were decreased in vacuolated (hypoxic) tissues. Water content, oxygen uptake, and octanoic-oxidase and succinic oxidase activities remained unchanged.

Bauer, L. H. Note on limits of high altitude. J. Aviation Med. 4:15-18 (Mar. 1933).

Bauer, R. O., and J. T. Gouryis. Lethality of simulated altitude for rabbits, normal and pretreated with tetraethylpyrophosphate of dibenamine. In Bauer, R. O., et al. (ed.). The effects of drug-induced alterations, pp. 44-49 Report No. 52-222, Wright Air Development Center. Aero Medical Lab., Wright-Patterson Air Force Base, Ohio (June 1952). Albino rabbits were exposed

successively to increasing simulated altitudes (25,000 to 40,000 feet). At each altitude, the animals were held for five minutes, then returned to ground level before renewed ascent. Chamber temperatures were recorded before, during, and after exposures. It was observed that environmental temperatures affected altitude tolerance considerably (25°C. representing the optimum temperature with regard to altitude tolerance). Preliminary treatment with adrenergic blocking agents, i.e., dibenamine, or with cholinergic potentiation drugs, i.e., tetraethylpyrophosphate, reduced altitude tolerance significantly.

Beard, E. J., L. D. Alexander, and T. W. Howell. Effects of various degrees of hypoxia on pulmonary and systemic hemodynamics in narcotized dogs. J. Aviation Med. 23(6):569-576, 625 (1952). Heart rate, respiratory rate, and femoral and pulmonary arterial pressures were studied in narcotized dogs breathing various oxygen-deficient gas mixtures. Inhaling a mixture of 8.5-percent oxygen in nitrogen for 30 minutes produced an increase in both systolic and diastolic systemic arterial pressures but no concomitant changes in the pulmonary arterial pressure. All

animals showed an increase in heart rate but no significant changes were noted in respiratory rate. When 5.8-percent oxygen in nitrogen was inhaled for short periods, pulse rate, respiratory rate, and arterial pressure gradually increased during the first five minutes. All animals survived for a ten-minute exposure without complications. Following sudden anoxia (produced by inhaling 99.6-percent nitrogen), pulse rate, respiratory rate, and femoral systolic and diastolic pressures increased and reached their maximums after one minute.

Benzil, G. Effect of vitamin B_{12} on the resistance to experimental hypoxia and on relative hepatosis. 11 Farmaco (Pavia) 16(3):144-151 (Mar. 1961). Mice given intraperitoneal injection of vitamin B_{12}, decompressed to 200 mm./Hg in 10 minutes, and kept at that level for 45 minutes., exhibited the same convulsive symptoms and fatal outcome as the controls. Histopathological examinations demonstrated that vitamin B_{12} was capable of decreasing the intensity of hypoxic hepatic steatosis. Quantitative chemical determinations of total hepatic lipids showed a

statistically important decrease in the lipid content of treated animals in comparison with the controls.

Berg, W. E., and S. F. Cook. Carbon dioxide production of humans at sea level and at low barometric pressures. Amer. J. Physiol. 147:217 (1946). The carbon dioxide elimination of humans, either under basal or non-basal conditions, is significantly decreased at a simulated altitude of 30,000 feet as compared with sea level values. Two methods of measuring the carbon dioxide elimination were used. One method involved collection of the expired gases in Douglas bags, the analysis being made at sea level with the Haldane gas analyzer. The second method employed a thermal conductivity analyzer for carbon dioxide in oxygen; the analyses and volume measurements were made directly at altitude. The average decreases of carbon dioxide elimination of basal and non-basal subjects at altitude were 6.4 and 8.6 percent respectively.

Berger, E. Y., M. Galdston, and S. A. Herwitz. Effect of anoxic anoxia on human kidney. J. Clin, Invest. 28:648 (1949).

Binet, L., D. Guing, and M. V. Strumya. Blood coagulation and anoxia. J. Physiol. (Paris) 48(3):393-395 (May-June 1956). Blood coagulation time was studied in the blood of anesthetized dogs breathing a 3.4-percent oxygen mixture for 40 minutes. Hypocapnic anoxic anoxia produced a moderate, but significant, acceleration of blood coagulation.

Blockley, W. V. Correlation of experimental and analytical data to define civil oxygen protection requirements above 40,000 feet. Aerospace Med. 33:1291-1297 (Nov. 1962).

Boi, Y. Studies on respiration and circulation in the cat: I. The influence of an acute anoxemia on respiration and circulation. J. Physiol. 55:43-49 (May 1921).

Boon, D. J., and S. F. Marotta. Environmental stresses and femoral arterial blood flow. J. Appl. Physiol. 19(3):472-478 (May 1964). Femoral arterial blood flow and related cardiopulmonary parameters were ascertained in 95 anesthetized dogs during exposure to heat, cold, altitude, hypoxia for two different time periods, and various combinations of these environments. Cold (1°C.) and

decompression (17, 300 feet) without hypoxia at room temperature (24°C) each depressed arterial blood flow significantly and equally, while the combination of decompression and cold caused a significant depression in flow which was less than either acting alone. Heat (38°C.) alone produced slight increases in arterial pressure and heart rate; however, heat in combination with altitude depressed the flow less than did altitude alone. Hypoxia (pO_2=75 mm. Hg), whether from decompression or breathing 10 percent 0_2 at ground level, increased blood flow while depressing femoral vascular resistance in all animals in cold, hot, or room temperatures. The greatest hypoxic increases in blood flow were noted immediately after decompression both at 24 and 38°C. While the smallest increase was noted with hypoxic exposure during the second period at a cold simulated altitude.

Brognoli, C., and B. Boles Carenini. On the possibility of influencing the alterations of the blind spot and of angioscotomata caused by anoxia of drugs (sic). Riv. Med. Aero (Roma) 15(2):274-286 (1952). The enlargement of the blind spot and of angioscotomata as induced by anoxia could be reduced by vasodilating drugs (amyl nitrite and

nicotinic acid). Parametric studies of normal subjects inhaling a mixture of low oxygen content revealed that generally the dilatation of both the blind spot and the angioscotoma is more or less proportional to the decrease of oxygen supply. In the majority of cases, amyl nitrite, administrated in a state of anoxia, restricted the area of the blind spot while it enlarged that of the angioscotoma In the majority of cases, nicotinic acid increased both the blind spot and the angioscotoma.

Bruner, H. On the stress limits of the human organism. Zeitschrift fur Flugwissenschaften (Braunschweig) 4(3-4):150-156 (Mar.-Apr. 1956). Aviation medicine must establish a qualitative evaluation of the sum total of flight stresses in which any shift would be reflected as a corresponding shift in the physcological index of reactions to stress. The selected indices must permit the establishment of physiological tolerance limits. The combination of measures of physiological tolerance limits and of environment stresses would allow the setting up of norms for complex stresses, duration of work, and work efficiency still within the limits of physiological tolerance. However, an objective method must first

be established for evaluating the individual capacity to see whether he is optionally trained and acclimatized to flight stresses. At present, aviation medicine is relatively well oriented on the amount of physical work in flight, the physiological thresholds, compensatory reactions, and critical thresholds to different flight stresses. Parallels are drawn with research along similar lines on stresses in the mining industry.

Bunge, J. Experimental studies on relation between high altitude convulsions and air temperatures. Luftfahrtmedizin 6:127 (1942)

Bures, J., and O. Buresdva. The anoxic terminal depolarization as an indicator of vulnerability of the cerebral cortex in anoxia and ischemia. Pfluger. Arch. Ges. Physiol. (Berlin). 264(4):325-334 (1957). The electrical polarity of the cerebral cortex surface (in rats about 20 millivolt positive) declines rapidly after a few minutes of total brain anoxia or ischemia. The latency of terminal depolarization approaches the latency of irreversible anoxic damage to the cerebral cortex. In hypothermic animals, terminal depolarization is delayed considerably. In the normothermic rat,

cortical polarity drops to zero after 15 minutes of ischemia. In the hypothermic animal, a residual polarity is still present at that time. Terminal depolarization is a new criterion for cortical survival time and is closer to revival time than other commonly employed criteria, e.g., loss of spontaneous electrical activity.

Bures, J. The influence of anoxia and asphyxia on the spreading EEG depression. Cesk. Fysiol. 6(4):467-471 (Nov. 1957). Young rats were subjected to the anoxic state or exposed to asphyxia for 45 to 75 seconds. Potentials were measured at various points on the cortex. During asphyxia, 45 seconds was the shortest time exposure that could maintain the widening depression; at this time, period negativity decreased within the first 15 seconds but then returned to normal. Above 45 seconds, widening of the depression increased with continuing exposure. Above 75 seconds, paroxysmal activity was observed. During anoxia, polarity dropped off to one-half of its original value, and the potential was depressed. In both asphyxia and anoxia there was an inhibition of oxidative processes.

C

Cahn, J., and M. Herold. Cardiac metabolism in anoxia. C. R. Soc. Biol. (Paris) 159(12):2133-2136 (1956). Anoxia produced by tracheal obstruction in rabbits and dogs resulted in a marked increase in cardiac debt and a lesser increase in femoral artery pressure followed by a decline to zero. Auriculo-ventricular dissociation and disturbances of the S-T interval, associated with bradycardia, were observed in some cases at near zero arterial pressure level. Anoxia produced an increase in blood glucose and lactate, a clearance in pyruvate (particularly at the terminal stage), 100-percent increase in the coefficient of extraction, 820 percent increase in the cardiac consumption of glucose, a regressive decrease in the coefficient of extraction and cardiac consumption of pyruvate myocardial production of lactate accompanied by a negative coefficient of extraction, and no significant change in myocardial glycogen.

Carenini, B. B. Studies on the behavior of the stereoscopic reuse (by means of the Wirt test) in conditions of a modified oxygen supply to visual apparatus. Riv. Med. Aero. (Roma) 18(3):754-770

(July-Sep. 1955). Wirt's test was used to evaluate the stereoscopic vision of 50 normal subjects between 18 and 36 years of age under hypoxic conditions. Hypoxia induced by breathing a mixture of 14.5 percent oxygen in nitrogen (a simulated altitude of 3,000 meters or 10,000 feet), did not reduce the initial values of the stereotest;on the contrary, it produced an increased value in 10 out of 50 subjects. Hypoxia induced by mixtures of 19.7 percent and 7.35 percent oxygen in nitrogen (altitudes of 6,000 and 8,000 meters or 19,000 and 26,500 feet), caused a decrease in stereoscopic acuity of about one half in all subjects, the others showing no significant change. The administration of pure oxygen at atmospheric pressure normalized stereotest values in subjects with initial normal stereoscopic acuity. The mechanism of action of hypoxia and hyperoxia in stereoscopic acuity is briefly discussed.

Cassin, S. Cerebral enzyme changes and tolerance to anoxia during maturation in the rabbit. Amer. Physiol. 201(3):440-442 (Sept. 1961). Rabbits varying in age from less than 24 hours to adulthood were studied. Newborn rabbits tolerate 30 to 35 minutes of anoxia. Adult rabbits withstand anoxia for 3 to 5 minutes.

Succinic dehydrogenase and cytochrome oxidase activities were very low at birth, but gradually increased for 15 to 18 days postnatally. Between 15 to 18 days, a critical period was reached in the development of these enzymes—adult levels of activity were attained. At this critical period the tolerance of the developing rabbit to anoxia becomes as poor as that of the adult. The increase in oxidative activity is in agreement with the hypothesis that metabolism of the mammal is transformed from predominantly anaerobic at birth to aerobic with maturation.

Cheymol, J. Lipoxidase and hypoxia. Therapie 18:341-362 (Mar. - Apr. 1963).

Creutzfeldt, O., A. Kasamatsu, and A Vaz-Ferreira. Activity changes of individual cortical neurons in acute anoxia and their relation to the EEG in cats. Pfluger. Arch. Ges. Physiol. (Berlin) 263(6):647-667 (1957). The electrical discharges of single cortical neurons were compared with the electroencephalogram (EEG) of cats during N_2 breathing for 50 to 60 seconds. After 10 to 20 seconds of N_2 breathing, the frequency of neuronal discharges and the frequency and amplitude of the fast beta-waves of the EEG were increased, while the 10/second wave of the EEG disappeared.

Neuronal discharges were decreased abruptly 10 to 20 seconds later, in correlation with alpha activation of the EEG. Discharges then ceased in half the neurons, while the remainder continued to discharge in irregular bursts corresponding to slow gamma-waves. All activity disappeared in the neurons 20 to 40 seconds after initiation of N_2 breathing, and in the EEG after 25 to 45 seconds. Recovery was complete 2 to 3 minutes after initiation of air breathing. Anoxic muscular convulsions were not reflected in either the EEG or in the activity of single neurons.

Creutzfeldt, O., A. Vaz-Ferriera, and A. Kasamatsu. The behavior of single cortical neurons under conditions of anoxia. Electroenceph. Clin. Neurophysiol. (Amsterdam) 7(4):662 (Nov. 1955). The action potentials of 40 single neurons of the sensory-motor cortex were recorded with micropipettes and their behavior was studied when the animal was given pure nitrogen through the trachea for 1 minute. The survival time of the neurons was 20 to 50 seconds (average 33 seconds), that of the electroencephalogram about 36 seconds. The recovery time of the cortical neurons (the reappearance of the first discharges after resumption of respiration with

fresh air) ranged between 10 and 120 seconds, normalization of the discharges usually occurring after 2 to 3 minutes.

D

Debias, D. A. Hormonal factors in the rats' tolerance to altitude. Amer. J. Physiol. 203:818-820 (Nov. 1962).

Debias, D. A., and K. E. Paschkis. Hormonal and nervous factors in the rat's tolerance to reduced barometric pressure. School of Aviation Med., Report No. 60-58, AF Aerospace Med Center, Brooks AFB, Texas (May 1960). A study was made of the effects of neuropharmacologic agents on the tolerance of adrenalectomized rats to a barometric pressure of 249 mm. Hg (equivalent to an altitude of 27,000 feet) for a period of 6 hours. Dibenamine, antrenyl, pendiomide, ditartrate, thorazine, and amphetamine did not improve tolerance. The survival time of adrenalestomized-thyrocdectomized rats was significantly increased (from 2.7 to 5.7 hours) by a dose of cortisol sodium succinate which failed to prolong survival of the adrenalectomized animal.

DeCorral, J. M., and A. Salces. Effect of anoxia on urinary secretion. Rev. Esp. Fisiol. 11(1):1-34 (Mar. 1955). Thirteen dogs rendered anoxic by breathing a mixture of 10 percent O_2 in N_2 exhibited no

changes in renal function. When 5 percent O_2 was used, urinary excretion increased but diminished with prolonged exposure to anoxia. During anoxic diuresis, the tubular reabsorption of water decreased in all animals and glomerular filtration increased in some and remained constant in others. Oliguria induced by prolonged anoxia coincided with a gradual increase in glomerular filtration. During diuresis in dogs, whereas water reabsorption remained decreased in some and returned to normal in others, a decrease in urinary volume was noted, but urinary concentration and density remained the same. Anoxia decreases tubular reabsorption of water and may even increase glomerular filtration, both changes causing anoxic diuresis which ceases when anoxia is prolonged. No changes were observed in blood chlorides, non-protein-nitrogen, or creatinine, nor were albumin, cylinders, or abnormal cells found in the urine.

Decorral, J. M., and A. Salces. Effect of anoxia on saline diuresis and phlorhizin polyuria. Rev. Esp. Fiziol. 11(1):35-48 (Mar. 1955). Phlorhizin-induced glycosuria and polyuria were not modified in dogs rendered anoxic by breathing a mixture of five-percent oxygen

in nitrogen. The decrease of diuresis in these animals may be attributed to decreased glomerular filtration rather than to anoxia. In saline-induced diuresis, an increase was noted in glomerular filtration simultaneously with a decrease in tubular reabsorption of water. No changes in polyuria were noted when the animals were exposed to anoxia. In both groups of polyuric animals, rebreathing of environmental air following anoxia gradually re-established the pre-anoxic diuretic and glomerular filtration rates.

Defranciscis, P. The spleen and the maximum tolerable altitude (ceiling level) in monkeys. Riv. Med. Aero. (Roma) 18(3):655-681 (July-Sept. 1955). Monkeys were decompressed at a rate of 333 meters per minute to various altitudes until a simulated altitude of 10,033 meters was reached. The maximum tolerable altitude (ceiling level) was determined as the time when the animal did not respond to stimulation (bell sound and slight electroshock). The persistence of consciousness for 30 minutes at 7000 meters was observed as the maximum tolerance to anoxia. With one exception, monkeys, showed a marked decrease of their ceiling level after splenectomy, a decrease not observed following simple laparotomy. The spleen

appears to have a specific and important function, hormonal in nature, indispensable in overcoming hypoxic deficiency.

Dimacco, G. Age and resistance to hypoxia. Riv. Med. Aero. (Roma) 19(2):311-315 (Apr.-June 1956). Adult guinea pigs of about 300 grams weight were more resistant to hypoxia (simulated altitude of 270 mm. Hg) than older animals weighing over 500 grams. These findings may be considered as an expression of the gradual decrease in the limitations of organic adaptation involving both central and peripheral processes.

Dimaria, G., A. Spina, and M. Deddatu. Studies on experimental hypoxia: III. Effect of adenosine-triphosphate (ATP) on the mvocardial fiber of guinea pigs subjected to chronic experimental hypoxia and tuberculin poisoning. G. Med. Fisiol. (Roma) 6(2):165-182 (1957). Adenosine triphosphate injected intramuscularly in guinea pigs subjected to chronic hypoxia was capable of notably limiting cardiac hypertrophy and degenerative lesions and also caused regression in the changes of the terminal phase of the electrocardiogram taken during the experiments.

Drabkin, O. L. Liver regeneration and cytochrome c metabolism: Influence of anoxia and of injection of cytochrome c. J. Biol. Chem. 171:409-417 (1947).

Eckman, M., and A. L. Barach. The effect on the vital capacity of a swift ascent to a simulated altitude of 36,000 feet. J. Aviation Med. 13:36-42 (1942).

Emerson, G. A., and E. J. Van Liere. Adrenin content of adrenals of cats subjected to anoxia. Proc. Soc. Exper. Biol. Med. 38:500-503 (1938).

Engel, G. L., et al. Syncopal reactions during simulated exposure to high altitude in decompression chamber. War. Med. 4:475-489 (1943).

F

Ferguson, F. P., D. Smith, and J. Barry. Hypokalemia in adrenalectomized dogs during acute decompression stress. Endocrinology 60(6):761-767 (June 1957). Unanesthetized, bilaterally adrenalectomized dogs maintained on cortisone, desoxycorticosterone acetate, or in a state of moderate adrenal insufficiency were exposed to a simulated altitude of 30,000 feet. Plasma K concentration had decreased by the end of the first 30 minutes and remained so for the duration of decompression. This effect is similar to that observed in intact dogs under the same conditions. Plasma Na remained unchanged (as it was in intact dogs) during the exposure. The adrenal glands do not mediate the hypokalemic response to high altitude.

Ferguson, F.P., D. C. Smith, and J. Q. Barry. The response of plasma potassium to acute decompression stress in adrenolectomized dogs. School of Aviation Med., AD 122 154, Randolph AFB Tex. (Nov. 1956). Bilaterally adrenalectomized dogs maintained on cortisone or disoxycortisosterone acetate, or animals in moderate adrenal insufficiency were decompressed to a simulated altitude of 30,000 feet for 90 minutes (three 30-minute periods). Plasma

potassium concentration consistently showed a marked decrease by the end of the first 30 minutes and remained depressed for the duration of decompression. This response is similar to that observed in intact dogs and indicates that (in this species) the hypokalemia of acute decompression stress is not mediated by the adrenal glands. As in intact dogs, plasma sodium concentration remained unchanged during decompression. In adrenalectomized animals decompression failed to produce the increase in hematocrit and the eosinopenia observed in intact dogs.

Ferguson, F. P., and D. C. Smith. Effects of acute decompression stress upon plasma and urinary potassium in adrenalectomized dogs. Abstract in Fed. Proc. 15(1[1]):62 (Mar. 1956). In 17 experiments upon cortisone-maintained bilaterally adrenalectomized dogs, plasma K concentration decreased by an average of 19.7 percent during 90 minutes exposure to 30,000 feet; in 16 experiments upon desoxycorticosterone acetate-maintained dogs, plasma K decreased by an average of 15.5 percent under the same conditions. Urinary excretion of potassium increased during hypoxia in both series of experiments. Exposure of cortisone-maintained dogs to severe

hypoxia resulted in an increase in plasma K concentration similar to that observed in intact animals under comparable conditions. The presence of the adrenal glands in dogs is not essential for the changes in plasma and urinary K observed during acute decompression stress.

Ferraloco, G. Experiments on carbohydrate metabolism at very high altitude. Arch. Sci. Biol. 13:109-126 (Jan. 1929).

Freeman, W. G., G. Pincus, and E. D. Glover. The excretion of neutral urinary steroids in stress. Endocrinology 35:215 (1944).

G

Gastaut, H., R. Naquet, and H. Regis. The comparative effects of anoxia on the electrical cortical activity and the reticular activity. C. R. Soc. Biol. (Paris) 151(12):2141-2144 (18 Dec. 1957). Electroencephalographic recordings were made on cats under anoxia, with injections of strychnine, and under anoxia and strychnine combined. Anoxia produces a decrease in activity starting in the cortex, and then progressing into the sub-cortical structures. Strychnine given after anoxia is started provokes an hypersynchronous discharge from the bulbar reticular formation which diminishes during further anoxia. Upon reoxygenation the discharge reappears in increased amplitude and frequency only to return to normal within a few minutes.

Gell, C. F. The problem of reduced barometric pressures. In Aviation Medicine Practice (NAVPERS 10839-A), pp. 7-28. Washington D. C.: Bureau of Medicine and Surgery, Bureau of Naval Personnel, 1955. This study covers the physiological effects of reduced barometric pressure and the methods and means by which flying personnel are provided with a normal or near-normal environment

at high altitude. Subjects include physics of the atmosphere, anoxia, aeroembolism, oxygen equipment in aviation, temperature variants and clothing, noxious gases, pressurized equipment, explosive decompression, and expansion of free gases in the intestinal tract, middle ear, and paranasal sinuses at altitude.

Gellham, E., and E. H. Lambert. The vasomotor system in anoxia and asphyxia. Urbana, Illinois: University of Illinois Press, (no date). Oxygen deficiency causes a rise of blood pressure only by action on the vasomotor centers through the carotid sinus nerves and the aortic nerves. The vasomotor center actually was depressed by oxygen want after denervation of the chemoreceptors and behaved much like the respiratory center during oxygen want. Fall of blood pressure caused by oxygen want after denervation of the chemoreceptors may result from a decrease in cardiac output, a depression of vasomotor tone which caused a reversal of blood pressure, or peripheral vasodilation.

Gellham, E., and C. Heymans. Differential action of anoxia, asphyxia, and CO_2 on normal and convulsive potentials. J. Neurophysiol. 11:261-273 (1948).

Gerard, R. W. Anoxia and neural metabolism. Arch. Neurol. Psychiat. 40:985-996 (1938).

Ghinozzi, G. P. Behavior of rectal temperature in rabbits subjected to reduced barometric pressure. Riv. Med. Aero. (Roma) 19(4):669-675 (Oct. -Dec. 1956). Rabbits decompressed to a simulated altitude of 7000 meters for one hour exhibited a 1.7°C. decrease in rectal temperature (from 40 to 38.3°C.). This decrease is attributed to anoxic anoxia induced by exposure to reduced barometric pressure.

Goldsmith, E. D., A. S. Gordon, and H. A. Charippen. Estrogens, thiourea, thiouracil (thiourea derivative) and tolerance of rats to simulated high altitudes (low barometric pressures). Endocrinology 36:364-369 (June 1945). Additional evidence shows the effectiveness of thiourea and thiouracil in increasing the resistance of rats to lowered barometric pressures. Daily injections of 0.05 mg. of estradiol dipropionate, estradiol benzoate, or diethylstilbesterol do not prolong the survival time of rats subjected to reduced

barometric pressures, nor do they enhance the protective powers of thiourea or thiouracil. These estrogens do not affect thyroid size or oxygen consumption but induce adrenal enlargement. The ability of females to tolerate low pressures better than males remains unexplained.

Gray, J. S. The time distribution of symptoms at 35,000 and 38,000 feet in the low pressure chamber. AF School of Aviation Med., Report No. 71, Randolph AFB, Texas (5 Sept. 1942).

Green, H. D., and R. Wegrin. Effects of asphyxia, anoxia, and myocardial ischemia on coronary blood flow. Amer. J. Physiol. 135:271 (1942).

H

Hale, H. B., and J. E. Keator. Comparison of eosinophil responses in human subjects during flights in aircraft decompressed to 40,000 feet and exposure to cold. Fed. Proc. 11(1[1]):63 (1952). Eosinophil fall values (which are proportional to the decrease of stress imposed during a test situation) were determined on a group of 100 medical officers. The average fall amounted to 8 percent per day under ordinary stress conditions. In a group of subjects flying in a C-47 type plane for 2 hours (with 30 minutes at 15,000 feet without supplemental oxygen) the eosinophil fall was 18 percent; in another group exposed to a simulated altitude of 40,000 feet (using oxygen equipment beyond 18,000 feet), the fall was 40 percent, in a third group exposed to -40°F. at ground level with a 5 m.p.h. wind (standard Air Force intermediate clothing assembly for cold protection), the fall amounted to 23 percent.

Hall, F. G., and K. D. Hall. Effects of adding carbon dioxide to inspired air on consciousness time of man at altitude. Proc. Soc. Exp. Biol. Med. 76:140-142 (1951).

Hall, F. G. Extra blood builds altitude tolerance. Aviation Week 52-33 (Mar. 27, 1950). Experiments have revealed that blood transfusions can raise a man's ability to withstand high altitudes. Five subjects who received an extra pint of blood could withstand 2,000 feet more altitude than usual in a decompression chamber. Four subjects who gave a pint of blood lost up to 2,000 feet of altitude resistance. In giving away some of their blood, the students cut down on their oxygen reserve. Altitude tolerance was measured by a subject's "interval of useful consciousness." He was usefully conscious as long as he could remain alert and perform certain tasks at a 35,000-foot altitude. Subjects were first tested while breathing pure oxygen; then they were tested while inhaling rarefied air at 35,000 feet.

Hall, F. G. Factors affecting consciousness time at altitude. Air Force Technical Report No. 6009 (Sept. 1950).

Hamberger, A., and H. Hyden. Inverse enzymatic changes in neurons and glia during increased function and hypoxia. J. Cell. Biol. 16:521-525 (Mar. 1963). Following stimulation of the vestibular

nerve in the rabbit, respiratory enzymic activities increased in Dexter's nerve cells. The anerobic glycolysis, measured as $10^{-4}\mu l$ CO_2 per hour per cell, was found to decrease concomitantly by 25 to 40 percent, suggesting a Pasteur effect. In the surrounding glia, the anerobic glycolysis increased and the respiratory enzyme activity decreased, suggesting a Crabtree effect. The evidence is dismissed for a regulatory metabolic mechanism operating between the neuron and its glia. Hypoxia of 8-percent oxygen caused an increased of both oxygen consumption and CO_2 production in the nerve cells but did not change the glia values.

Hamberger, R. J. Hemoglobin electrophoresis in hypoxia. Aeromed. Acta 5:399-402 (1956-1957). Variations in the synthesis of hemoglobin result in different forms of the hemoglobin. Although to this point the established variations were hereditary, the possibility exists that other factors, such as prolonged hypoxia, may also interfere with the normal hemoglobin synthesis. Deviations of the hemoglobin molecule were investigated in rabbits kept for 2 to 3 weeks (7 hours a day) at a 7000-meter simulated altitude. Hemoglobin displacement was measured with paper electrophoresis

by scanning the paper with a photoelectric cell and reflected light. No changes in hemoglobin mobility as a result of hypoxia could be demonstrated.

Haneveld, A. van. The electroencephalogram after prolonged brain asphyxiation. J. Neurophysicl. 10:361-370 (1947).

Harrison, T.R., and A. Blalock. The regulation of circulation: VI: The effects of severe anoxemia of short duration on the cardiac output of morphinized dogs and trained unnarcotized dogs. Amer. J. Physiol 80:169-178 (Mar. 1927).

Helmholy, H. F., J. B. Bateman, and W. M. Boothby. The effects of altitude anoxia on the respiratory process. Aviation Med. 15:366-380 (Dec. 1944). Some results are given on the analysis of alveolar gas from persons breathing air at simulated altitudes up to 22,000 feet (6,700 meters) or pure oxygen up to 42,000 feet (12,800 meters). The data are amenable to representation in simple diagrams for discussion of several phenomena. While an alveolar air equation covers a whole series of physically possible states, graphically presented experimental data show the physiological state.

Hiestand, W. A., F. W. Stemler, and R. L. Jasper. Increased anoxic resistance resulting from short period heat adaptation. Proc. Soc. Exper. Biol. Med. 88 (1): 94-95 (Jan. 1955). Mice exposed to heat (36 to 37°C.) in an incubator for periods of 10 and 14 days were drowned in water at body temperature (approximately). Heat adaptation was found to increase anoxic resistance to drowning (survival time) by 14.5 and 28.9 percent after 10 and 14 days respectively. The effect is attributed to lowered basal oxygen requirements in heat-adapted animals.

J

Jankowski, W., and S. Irvankiewiez. Hearing in acute oxygen deficiency. Otalatyng. Pol. 9(1):15-23 (1955). Hearing thresholds of 71 pilots were not modified by exposure to a simulated altitude of 6500 meters in a decompression chamber. After exposure to sound intensities of 60 and 80 decibels for 5 minutes, 25 pilots showed an average increase of 10 decibels in their hearing threshold which returned to normal within 20 to 60 seconds. Under anoxic conditions, with a sound intensity of 80 decibels for 5 minutes, an average decrease of 27.6 decibels in hearing was noted, which was compensated after 3 minutes.

Joels, N., and E. Neil. The influence of anoxia and hypercapnia, separately and in combination, on chemoreceptors' impulse discharge. J. Physiol. (London) 155:45-46 (1961). Experiments were designed to test whether the combination of anoxia and hypercapnia exerted a greater than additive effect on the chemoreceptor response of the perfused carotid body of a cat.

Johnson, L. F. The effect of decreased barometric pressure on maximum pressure-volume relationships of the human respiratory system. Aerospace Med., 35:637-642 (July 1964). Maximum expiratory and inspiratory pressures and the resulting lung-volume changes were simultaneously recorded at ground level (approximately 747 mm. Hg) and at an altitude of 30,000-feet (pressure: 225 mm. Hg). Lung-volume changes were greater at 30,000 feet that at ground level. The area of the maximum pressure-volume diagram at 30,000 feet was 79 percent of the same diagram at ground level.

Keyes, G. H., and V. C. Kelley. Glucose tolerance of dogs as altered by atmospheric decompression. Amer. J. Physiol. 158:358-366 (no date). The effect of adrenalin was studied under various conditions. Stimulation of the sympathico-adrenal system plays only a minor role in most cases where a glucose tolerance test is performed on dogs at a simulated altitude of 24,000 feet. Apparently, sufficient oxygen exists at this altitude to allow functioning of the enzymes involved in glucose metabolism so that, actually, a more rapid formation of glycogen occurs than at ground level. An increased production from the adrenal cortex is the most predominant factor. Although delayed return of the blood glucose to the base line level occurs after injecting glucose at a simulated altitude of 24,000 feet, careful perusal of the data presented indicates an increase in glucose tolerance. The injected glucose is converted to glycogen more rapidly than at ground level and the high glucose levels thereafter are due to gluconeogensis from fat and protein brought about by the increased production of hormones by the adrenal cortex. Adrenalin may play a minor role

in certain cases where the blood glucose level is maintained at markedly increased levels.

Kingma, H., and C. Langen, The blood-pressure diagram in the low pressure chamber at various simulated altitudes. Aeromed. Acta. 4:105-110 (1955). A blood-pressure diagram is obtained by registering a subject's blood pressure before exercise, after he has performed 20 deep knee bends within 25 seconds, and every minute for 10 minutes while he remains standing. If the subject collapses during the last stage, the blood pressure is registered directly after the collapse while he is in a horizontal position. At low atmospheric pressure (in a low-pressure chamber), the collapse is evoked more readily. Subjects with normal blood-pressure diagrams at sea level vary greatly in the extent of circulatory disturbances in response to this test at simulated altitudes. Blood-pressure diagrams of three subjects at sea level and at altitude are analyzed.

Konstantinov, V. A. The significance of the inhibition of the central nervous system in anoxia. Pat. Fiziol Eksp. Ter. 4(2):58-62

(Mar. -Apr. 1960). Hypoxia was induced in white mice by placing them in hermetically sealed boxes of 100 cubic centimeters volume. If subjects were removed from the container 20 to 40 seconds before the appearance of terminal breaths, respiration was resumed and the animal survived. The threshold survival time for mice in hermetic containers averaged between 12 to 13 minutes. Repeated exposure to hypoxia in the container prolongs the survival time since inhibition of the central ne vous system is developed during hypoxia. While there is still sufficiently intensive trace inhibition present, repetition(10 times) of hypoxic exposures leads, as a result of summation, to more profound inhibition of the central nervous system. The threshold survival time after repeated exposures exceeded initial threshold values 8 to 9 times.

L

Lamb, L.E. Influence of aerospace flight on the normal cardiovascular system; stresses and effects. Amer. J. Physiol 6(1):8-18 (July 1960).

Lance, J.S., and H. Latta. Hypoxia, atelectasis, and pulmonary edema; the role of hypoxia in the production of pulmonary edema, atelectasis, and hyaline membranes. Arch. Path. (Chicago) 75:373-7 (April 1963). Adult rats subjected to hypoxia (47 to 5 percent oxygen for 24 hours in a closed box with a controlled constant flow of oxygen) had lung weights significantly heavier than those of control animals. The increase was more marked in the animals dying during a 24-hour period than in those surviving a full day. The increase amounted to nearly one-third of the average normal lung weight, and although no histological difference between hypoxic and control lungs were detected subtle edema and, probably, hyperemia may be responsible for the increased weight. Newborn rats exposed to more severe hypoxia (3 to 4 percent oxygen) frequently showed focal atelectasis and animals dying spontaneously often showed pulmonary edema. The increased incidence of pulmonary edema in newborn rats dying during hypoxia suggests that heart failure

may have been a contributory cause. Prolonged hypoxia in the newborn and the adult favors the production of atelectasis and pulmonary edema but is not sufficient alone to produce hyaline membranes. The direct introduction into the lung of fresh blood plasma without clotting inhibitors does not produce hyaline membranes. Additional factors, possibly both intrinsic and extrinsic, seem to be necessary.

Lauer, N.V., M.M. Koganovskaya, O.P. Kostenko, and M.S. Bondarevskiy. AFSC N65-17760, Foreign Technology Div., Wright-Patterson AFB, Ohio. The effect of hypoxia was studied in young and mature dogs. The animals were placed in a decompression chamber, and the simulated altitude was varied from sea level to 15,000 meters. Electrocardiograms were taken at every 1000 meters. During the first few days after birth, the animals subjected to hypoxia did not show any deviations from the normal electrocardiogram. As the animals matured, cardiac effects were registered in certain electrocardiographic variations: the T-wave amplitude was low; and the S-T segment and the T-wave were increased. These deviations do not indicate a disturbance in the cardiac function, but suggest a different cardiac structure during growth and development of the body and a specific type of tissue metabolism.

Le Blond, C. P. Increased resistance to anoxia after thyroidectomy and after treatment with thiourea. Proc. Soc. Exper. Biol. Med. 55:114 (1944).

Lewis, B. M., and L. Dexter. Effects of acute hypoxia on the circulation of the dog. Amer. J. Med. 12:109 (Jan. 1952).

Lewis, R. A., G. W. Thorn, G. F. Koepf, and S. S. Dorrance. The role of the adrenal cortex in acute anoxia. J. Clin. Invest. 21:33-46 (1942).

Lipin, J. L., and W. V. Whitehorn. Circulatory adjustments to reduced barometric pressure. AF School of Aviation Med., Project Report No. 3, Randolph AFB, Texas (1951). Anesthetized dogs exposed to a simulated altitude of 35,000 feet (178.7 mm. Hg) with oxygen inhalation show no significant changes in heart rate, stroke volume, cardiac output, and systolic, diastolic, mean, and pulse pressures. Skin temperatures are significantly reduced and indicate a reduction in peripheral blood flow. The factors responsible for the reduction in peripheral circulation have not been determined but vasomotor reflexes originating in the distended gastrointestinal tract and accessory air sinuses or accumulations of extravascular gas in body tissues may be responsible.

Lorentzen, Vogt F. Non-esterified fatty acids in venous blood under different experimental conditions. Aerospace Med. 35:649-652 (July 1964). Non-esterified fatty acids (NEFA) were determined during and after the following conditions; exercise to exhaustion by trained and untrained subjects, standardized moderate exercise, hypoxia (20,000 feet), exercise and hypoxia, hypercapnia, hypocapnia alkalosis and breathing pure oxygen. Some typical changes are described. Great variations in the normals and many irregular curves (with peaks and dips) were found. NEFA in blood may not be a reliable measure of fatty acid metabolism.

Luft, U.C. In Armstrong, H.G. (ed.). Aerospace Medicine, p. 130. Baltimore: Williams and Wilkins Co., 1961. Changes in the electrocardiogram (in Lead II) occur in an individual who has been at an altitude of 16,400 feet (5,000 meters) for five minutes. The heart rate increases and the height of the T-wave reduces from 0.46 to 0.33 mv. After one minute at an altitude of 24,600 feet (7,500 meters), the T-wave decreased to 0.23 mv., the ST segment showed a slight depression, and the P-wave was higher. Following the administration of oxygen, all these changes disappeared within thirty seconds.

Luria, L. Respiratory modifications in acute hypoxia caused by rebreathing. Boll. Soc. Ital. Biol. Med. Sper. 31(1-2):41-43 (Jan.-Feb. 1955). Nonathletes and athletes, including mountain climbers, rebreathed a mixture of 8 percent O_2 in N_2 (simulated altitude of 6800 meters), decreasing after 3 to 4 minutes to 4.5-to 5.5-percent O_2 in N_2 (simulated altitude of 8,000-9,000 meters). Nonathletes demonstrated an increase in respiratory amplitude during the first minutes of the experiment. After 3 to 4 minutes, respiratory frequency increased by 35 percent and pulmonary ventilation showed a gradual increase and finally became stationary. In athletes, the respiratory response to hypoxia was more pronounced; an increase was exhibited in pulmonary ventilation which was parallel to an increase in respiratory amplitude and, with slight modification, to respiratory frequency.

MacKensie, C.G., et al. Duration of consciousness in anoxia at high altitude. J. Aviation Med. 16:156-174 (1945).

Magill, A.M., and J. Marbarger. Survival time during exposure to severe hypoxia in the rat treated with adrenocorticotrophic hormone. J. Aviation Med. 26(4):308-318 (Aug. 1955). Survival time and cumulative mortality rates of male and female albino rats exposed to severe hypoxic stress were studied in control (group I), altitude-adapted animals (group II), animals treated with a total dose of 3.5 units of ACTH (group III), animals treated with a total dose of 10.5 units ACTH (group IV). Group II was exposed to 18,000 feet simulated altitude for 3 weeks prior to the survival-time study. In the experiments, the animals were decompressed at a rate of approximately 2000 feet per minute to a simulated altitude of 35,000 feet. Survival time data indicated the appearance of a trend toward greater than normal-time values in group IV. Group III did not have a survival time or mortality rate which differed appreciably from group I. For the initial 5 minutes of exposure, group II had a lower mortality rate than any of the other groups; cumulative death rates exceeded those of

group IV. However, the females seemed to have a slightly greater tolerance to hypoxic ex. sure than the males.

Malkin, V.B., A.N. Razumeyev, and G.V. Izasimov. An investigation of the bioelectric activity of the cerebral cortex and certain subcortical formations in acute hypoxia. AFSC.N65-17767, Foreign Technology Division, Wright-Patterson AFB, Ohio. Acute hypoxia was induced in rabbits at various simulated altitudes in a low-pressure chamber. The animals had permanent electrodes implanted into the sensory-motor areas of the brain. Three phases in the change of the brain potentials under conditions of the increasing hypoxic hypoxia were observed; stimulation of the high-frequency impulses, predominance of slow waves of large amplitude, and depression of potentials. These phases were evident in the electroencephalograms of the sensory-motor areas of the cortex, the reticular formation, and the hypothalamus. No changes were noted in the potentials of the hippocampus. The effect of acute hypoxia of short duration which causes a complete depression of potentials through the well defined phases cannot be reduced to a simple mechanism of radiation of impulses.

Marcotte-Boy, G., and J. Cheymol. Effect of moderate hypoxemia (simulated altitude of 7000 meters) on the distribution of acid-soluble phosphorus in the blood. Bull. Soc. Chim. Biol. (Paris) 37(2-3):383-386 1955. Rabbits decompressed to a simulated altitude of 7000 meters for three hours demonstrated a decrease in acid-soluble phosphorus compounds in the blood. Decreases of 47 percent were observed in blood adenosinediphosphate and adenosinetriphosphate, and 24 percent in hexosephosphates; an increase of 10 percent was noted in blood glycerophosphate content.

Merrill, J.M., J. Lemley-Stone, and G.R. Meneely. Effect of acute anoxia on the glutamic oxaloacetic transaminase content of the myocardium of the rat. Amer. J. Physiol. 190(3):522-524 (Sept. 1957). Transaminase activity in tissues and serum was determined in a group of rats subjected to anoxia and in a control group of animals. A 27 percent decrease occurred in the transaminase activity of the anoxic myocardial tissue without any appreciable change in serum activity. Other tissues which were studied showed that anoxia produces varying decrements in transaminase activity. In vitro studies of tissue taken from anoxic animals indicate that the loss of transaminase activity is not caused by loss or destruction of its coenzyme pyridoxal phosphate.

Middlesworth, L. Van. Metabolism of I^{131} in severe anoxic anoxia. Science 110:120 (1949).

Mumenthaler, M. Effect of hypoxia on the result of the Rorschach test. Med. Aero. (Paris) 10(1):31-36 (1955). Forty-seven student pilots (subjected to a Rorschach test 19 months earlier under normal conditions) were tested under conditions of hypoxia produced in a decompression chamber at a simulated altitude of 6000 meters. The frequency of emotionally indicative responses appearing normally was found to be increased under hypoxia from 60 to 150 instances. The responses were dominated by the universe (sea, earth, and elements), the primitive states of human development (ancient history and myths), an emphasis on external and material qualities (i.e. rigidity), elements of rotation and the dance, heaviness (including fatigue), grotesque elements, and vague and uncertain identifications. Two or more of these qualities were often combined in one response. Responses tended to emphasize detail and stationary position. The fundamental intellectual functions of the subjects, indicated by factors such as reaction time and percentage of animals (sic), were not impaired by lack of oxygen. The differences noted between responses

in the normal and hypoxic states (manifested in the latter by a sense of detachment from reality) were considered to be indicative of a general psychic reaction which is not peculiar to hypoxia.

N

Nagg, Z., and J. Skolnik. The effect of cocarboxylase on cardiac output in acute hypoxia. Acta Med. Acad. Sci. Hung. 19:59-66 (1963).

Nielsen, M., and H. Smith. Studies on the regulation of respiration in acute hypoxia; with an appendix on respiratory control during prolonged hypoxia. Acta Physiol. Scand. 24(4):293-313 (1952). In order to determine the effect of CO_2 on pulmonary ventilation during hypoxia, two subjects breathed mixtures of O_2, N_2 and CO_2, with O_2 partial pressure adjusted so as to keep the alveolar O_2 level constant in the various hypoxic stages. CO_2 breathing in the hypoxic state did not affect pulmonary ventilation until a certain threshold value of aveolar CO_2 was reached. Beyond the threshold value, an increase in p CO_2 had a greater effect than uncer normal conditions. The threshold value was found to be constant at the various stages of hypoxia and is, therefore, believed to be identical with the CO_2 threshold of the respiratory center. Low O_2 pressure during acclimatization may cause a primary increase in ventilation due to an increased activity of the center. In prolonged hypoxia, the CO_2 threshold is decreased.

Ni.na, L.F. Anoxia. Amer. Rev. Physiol. 10:305-314 (1948).

Northrup, D.W., and E.J. Van Liere. The effect of anoxia on the absorption of glucose and of glycine from the small intestine. Amer. J. Physiol. 2:288- (Sept. 1941). Anoxia up to and including 53 mm. Hg partial pressure of oxygen does not alter significantly the absorption of glucose from the small intestine of the dog. Anoxia at 53 mm. Hg oxygen tension, but not higher partial pressures, significantly depress the absorption of glycine. The experiments suggest that an oxidative process may be directly involved in the absorption of glycine. The significance of the lack of effect of anoxia on glucose absorption is discussed.

P

Pescador, L. Changes of heart in high altitude flights. Rev. Clin. Esp. 2:449-453 (1 May 1941).

Phillips, N.E., P.A. Saxon, and F.H. Quimby. Effects of humidity and temperature on the survival of albino mice exposed to low atmospheric pressure. Amer. J. Physiol. 161:307 (1950).

Pratt, A.J., D. Smith, and F. Ferguson. Role of the adrenal gland in the response of plasma potassium of the rat to moderate and severe hypoxia. Endocrinology 57(4):450-455 (Oct. 1955). Rats decompressed to simulated altitudes (25,000 to 35,000 feet) for 30 minutes show a reduction in plasma potassium concentration (up to 22 percent). No change in the plasma potassium concentration takes place in adrenalectomized rats after decompression to 30,000 feet for 30 minutes. Administration of adrenalin to the adrenalectomized rat reduces the plasma potassium level; decompression of these animals produces no further reduction in potassium levels. If either intact or adrenalectomized rats are exposed to an altitude of 40,000 feet until respiratory collapse occurs, the plasma potassium concentration rises

significantly. The adrenal medulla is implicated in the changes in plasma potassium which occur during moderate decompression but not in the changes during severe decompression.

R

Rahn, H., and A. B. Otis. Continuous analysis of alveolar gas composition during work, hypercapnea, hyperpnea, and anoxia. J. Appl. Physiol. 1:717-724 (1949). The O_2-CO_2 diagram offers a new approach to the quantitative description of various respiratory phenomena, since it allows the simultaneous visualization of alveolar oxygen, carbon dioxide respiratory quotient, and ventilation. This approach is made particularly useful with the continuous recording of alveolar gas composition. Experiments have been performed which indicate that the alveolar gas concentration can be varied in certain directions only and along certain pathways. This in a large measure is controlled by the changes in CO_2 output which varied with the relative ventilation. Diagrams show the principal pathways that have been observed during hyperpnea, anoxic hypoventilation, exercise, and CO_2 breathing as well as the pathways of recovery.

Rahn, H., and A. B. Otis. Alveolar air during simulated flights to high altitudes. Amer. J. Physiol. 150:202 (1947).

Rossi, N. Myocardial cytochrome oxidase in experimental hypoxia. Acta Anaesth. (Padova) 8(3):189-196 (May-June 1957). Cytochrome oxidase was found to persist in the myocardium of hypoxic rats examined after death. Moreover, it appears in an unaltered so-called indophenoloxidase form.

S

Saha, H. Observations on some endocrine changes under low atmospheric pressure simulating high altitude. J. Indian Med. Assoc. 23(10):428-41 (July 1954). Rats exposed to simulated altitudes of 30,000 feet two hours a day for periods up to 12 days showed a generalized disintegration of the suprarenal cortex, a degeneration of the spermatogenic element and of the interstitial cells of the testes, a marked proliferation of basophilic cells (with a proportional diminution of acidophils) in the pituitary, and body weight losses as high as 13 percent. Intramuscular administration of vitamin E increased the survival period and retarded the fall in body weight and disintegration of the suprarenal cortex. The vitamin preserved the interstitial cells of the testes but had doubtful protective effects upon the spermatogenic cord.

Saito, M. Experimental study on the tissue water and electrolyte balance during acute induced anoxic anoxia. Mie. Med. J. 10(3):259-281 (Nov. 1960). Anoxic anoxia induced in 15 rabbits by partial obstruction of the air passage produced an increase in plasma potassium and magnesium levels and an increase in the water content of the lower

and abdominal muscles. Magnesium content in the liver and abdominal muscles decreased, as did the potassium content in the brain, abdominal muscles, and liver. No significant variations were measured in renal potassium content or in the sodium and chloride levels of the plasma and tissues. Potassium tended to shift from the intracellular to the extracellular space during anoxic anoxia, especially in the liver.

Schiller, A. A., and G. N. Wood. Disappearance rate of fluorescein conjugated plasma protein from the circulation of hypoxic rats. Fed. Proc. 11(1^{I}):139 (1952). Fluorescein conjugated homologous plasma proteins were injected intravenously into rats and separate groups were exposed for 3 hours to simulated altitudes of 18,000, 28,000, 30,000 and 34,000 feet. Blood samples (from tail veins) taken prior to and following altitude exposure were examined fluorophotometrically for concentrations of the fluorescein label. The disappearance rate in the altitude-exposed animals was 3.9 ±0.8 hours, as compared to 4.0 ±0.9 hours in the ground controls; there was little difference among the various experimental groups. Anoxia (up to pO_2= 25 mm Hg. and

30-percent oxygen-hemoglobin saturation) does not produce hemodynamic or permeability changes which would alter transcapillary passage of plasma proteins.

Schultz, G. O. The problem of vacuolation in the central hepatic lobules and a new procedure for liver perfusion: An experimental animal study of concern to aviation pathology on the problem of acute death from exposure to high altitudes Arztliche Forschung (Munchen) 8(2):78-84; (10 Feb. 1954). The process of vacuolic degeneration of the central liver cells observed after death from exposure to high altitude was experimentally investigated in animal species, in situ and extirpated...were undertaken and different gases added to the solution (sic). The significance of colloid bodies was studied. The results revealed that the animal organism may produce identical responses to a multitude of influences. On the basis of frequent observations of vacuolic degeneration by enzymatic block, and because of the ease with which this block appears after addition of CO_2 to the solution perfused through the liver, heightened CO_2 stasis resulting from a metabolic disturbance is responsible for the vacuolic degeneration observed in high altitude deaths.

Shuba, M. F. Influence of anoxia on the physical electrotonus of smooth muscle. AFSC N65-17772, Foreign Technology Div., Wright-Patterson AFB, Ohio. The smooth sphincter muscle of the frog's stomach, with polarizing and lead electrodes applied, was mounted in a humid hermetically sealed chamber. Anoxic conditions were established by passing pure nitrogen through the chamber. Potassium cyanide was used as a cell respiration inhibitor. Therefore, the tissue, lost its ability to reduce oxygen and oxygen starvation set in. After the tenth minute of cyanide treatment of the muscle, the amplitude of the negative local potential had diminished markedly and gradually decreased to zero value. This decrease was found to be a reversible reaction and the amplitude could be restored to original value. The amplitude of the electronic potential depends upon the permeability of the protoplasmic membrane.

Simonson, E. Experimented hypoxemia in older and younger healthy men. J. Appl. Physiol. 16(4):639-640 (July 1961). Arterial O_2 saturation was measured by means of an earlobe oximeter in 68 older (mean age 59.5 years) and 58 younger (mean age 23.4 years) healthy men. While

breathing a 10 percent O_2-90 percent N_2 mixture for a period of 10 minutes, the drop of the arterial oxygen saturation was more pronounced in the older men and the difference in reaction was highly significant statistically.

Stupfel, M., and J. Roffi. Effect of anoxia and different levels of carbon dioxide on the nonadrenaline and adrenaline content of the rat brain. C.R. Soc. Biol. (Paris) 155(2):237-240:1960. Fifty-nine adult rats exposed for 1 hour to a hypoxic atmosphere (5 to 10 percent O_2) showed a decrease of 23 percent in the level of cerebral nonadrenaline content. Atmospheres of 5, 10, or 20 percent CO_2 produced no modifications in the level of cerebral catecholamide. The fluorometric method (Von Eurler and Flading) was used to determine cerebral nonadrenaline and adrenaline contents in vitro. Sex of the animal produced no significant variations, although younger animals tend to have lower levels.

Suzar, O., and R.W. Gerard. Anoxia and brain potential. J. Neurophysiol. 1:558-572 (1938).

T

Thorn, W. Brain metabolism during acute anoxia, acute ischemia, and during recovery. Pfluger. Arch. Ges. Physiol. (Berlin), 261(4):334-360 (1955). A rapid rise in inorganic phosphate, fructose diphosphate, and ADP, and a slow decrease in adenosine triphosphate were observed in the brains of rabbits during short periods of cerebral ischemia or respiratory asphyxia (5 percent CO_2 in N_2). Recovery after cessation of anoxia was rapid. Lactic acid increased slowly during anoxia and was still elevated 30 minutes after the end of the anoxic period: Labile phosphate, in the form of phosphocreatine, is considered to be the essential factor in the recovery. As a quick energy source, labile phosphate fell by 50 percent within a few seconds after initiation of anoxia: Its disappearance within two minutes was followed shortly by the death of the animal. Blood pressure, pulse rate, and the electric potential patterns of the brain and heart were all altered by anoxia.

Tomsovic, M. The effect of anoxia upon learning and reversal of a position habit in the white rat. Ann Arbor, Michigan: Univ. Microfilms Publications No. 10,556, 1955. An experiment was conducted to study

the effects of anoxia (6 hours at a simulated altitude of 30,000 feet) on the capacity of rats one day after exposure to learn and reverse a position habit in a single T maze with a 23-1/2 hour water deprivation as a drive. A statistically insignificant increase was observed in the number of trials required for learning and the number of errors made by experimental animals. Microscopic examination of the brains of anoxic animals revealed a statistically insignificant decrease in mean cortical cell concentration (lamina II of area 10), but no distinguishing necrosis. Anoxia had no effect on weight change, alterations in the daily water intake, or group running time. Turning preferences prior to training had no effect on learning in experimental animals.

W

Wayne, H.H. A clinical comparison of the symptoms of hypoxia and hyperventilation. School of Aviation Med., Ad 152817, Randolph AFB, Texas (no date). A total of 183 subjects were exposed to hypoxia at 25,000 feet and hyperventilation at ground level. End point was muscular incoordination as evidenced by illegibility of handwriting. Symptoms were recorded in all cases. Tabulation of symptom frequency revealed that it was not possible on clinical grounds to differentiate between hypoxia and hyperventilation. The symptoms of hypoxia and hyperventilation are similar since hyperventilation invariably accompanies any significant degree of hypoxia. Recommendations are presented which will help the pilot having symptoms at altitude to take proper corrective action even though he may not be immediately aware of whether he is hypoxic or hyperventilating.

Wiggers, C.P. Cardiac adaptation in acute progressive anoxia. Ann. Int. Med. 14:1237-2347 (Jan. 1941).

Y

Yesinick, L., and E. Gellhorn. Studies of increased intracranial pressure and its effect during anoxia and hypoglycemia. Amer. J. Physiol. 1:185-194 (Dec. 1939). The intracranial pressure effective in the Cushing reaction is a function of the blood pressure-intracranial pressure differential and does not depend upon the absolute intracranial pressure difference. These observations and the fact that increased intracranial pressure raises the blood pressure in dogs deprived of their buffer nerves (inhalation of nitrogen causes a fall in blood pressure) indicate that the effects of intracranial pressure are due to asphyxia of the medulla rather than to anoxia. The inhalation of 7-to 8-percent oxygen potentiates the blood pressure response to raised intracranial pressure in the anesthetized dog. The effect increases with increased duration of the period of anoxia. This potentiation persists in the absence of the buffer nerves and is reversible by the inhalation of air. Hypoglycemia also potentiates the blood pressure response to raised intracranial pressure in the anesthetized dog. The effect increases progressively with falling blood sugar and, likewise, persists in the absence of the buffer nerves, but is reversible by injection of glucose.

Yurugi, R., and T. Totsuka. Analysis of fatigue during stress of low atmospheric pressure: III. On the change of inorganic electrolytes in the blood and brain of rats during stress of low atmospheric pressure. Japanese Aero-Medical Group, Report No. 38:12 (20 Mar. 1960). After rats had been exposed to a simulated altitude of 7000 meters for several hours, their sera, red blood cells, and brains were analyzed for electrolytes by flame photometry. An increase in potassium content and a lowering of the sodium-potassium ratio were noted in the sera, red blood cells and brains. The chloride content of the sera and red blood cells and the calcium content of the sera, red blood cells, and brains were decreased.

III, DECOMPRESSION

A

Achiary, A., A. Cabazon, V. Andre, and J. Richet. Rapid and explosive decompression in flight: study of 15 cases. Med. Aero. (Paris) 11(1):73-86(1956). Fifteen cases of decompression which occurred in fighter aircraft at high altitude are described. No serious effect of decompression on either men or equipment was observed. Equipment should be provided for protection against extreme cold and for automatic supply of pressurized oxygen.

Adler, H. F. Neurocirculatory collapse at altitude. AF School of Aviation Med., Special Report, Randolph AFB, Texas (June 1950). This study provides a summary of knowledge of neurocirculatory collapse at altitude.

Allan, J. H. Decompression disease of bone. Aviation Med.,14:105-111 (June 1943). Available literature on changes in the skeletal system resulting from decompression illness is reviewed. Any obliteration process interferring with blood supply will initiate a process of aseptic necrosis if near a joint or will initiate the production of a bone infarct if occurring in the shaft of the bone. The late effects of this process (aseptic necrosis involving hips and shoulders, medullary calcification in the diaphyseal end of the long bones, and hypertrophic arthritis)

are recognizable roentgenographically. Not all these effects need be present in an individual to justify the diagnosis. Aseptic necrosis with osteoarthritis may occur without medullary calcification. Joint changes are more frequently present than changes in the long bones. The recognition of these bone changes is of paramount interest in time of war, as the incidence of symptoms of decompression illness associated with high-altitude flights is on the increase.

B

Bancroft, R. W. Intraabdominal pressure relationships in the anesthetized dog during rapid decompression. School of Aviation Med., AD 92 257, Randolph AFB, Texas (Oct. 1955). This investigation attempts to determine the increase in abdominal pressures and the possible effect on the circulation. The gastric, abdominal, vena caval, and arterial pressures were measured simultaneously in dogs during and following rapid decompressions to simulated altitudes of 45,000 to 72,000 feet. Gastric pressures increased during the decompressions, the greatest increases occurring at the most extreme altitudes. After a few seconds at these peak altitudes, the gastric pressure tended to decline. The abdominal venous pressures were relatively unaffected during rapid decompressions to altitudes below 62,000 feet but increased following decompression, coinciding with a drop in arterial pressure. With decompressions to altitudes above 62,000 feet, abdominal venous pressure increased rapidly both during and following the decompressions, again coinciding with an almost immediated drop in arterial pressure. The increased gastric pressure during decompression appeared to have little effect on the systemic circulation compared to the overwhelming effect of anoxia and possibly water vapor pressure in the vena cava at altitudes above 62,000 feet.

Behnke, A. R. Decompression sickness. Military Med. 117(3):257-271 (Sept. 1955). Decompression sickness arises from the presence of nascent gas bubbles following too rapid decompression from ground level to high altitudes. The bubbles, chiefly intravascular, act as diffuse massive emboli to obstruct circulation and produce remarkably protean manifestations. Prominent are pains (bends), respiratory distress progressing to asphyxia (chokes), circulatory obstruction giving rise to central and peripheral circulation failure (shock), spastic paralysis referable to spinal cord injury, and chronic bone lesions. The mechanism of recompression is noted, and case histories are reported, illustrating the recurrent clinical error of inadequate recompression in terms of duration and degree of pressure required. In addition, a comparison of altitude and diving decompression sickness is given.

Bierman, H. R. Decompression illness. Washington Univ. Med. Alumni Quart. 6:169-178 (July 1943).

Bridge, E. V., F. M. Henry, S. F. Cook, O. L. Williams, W. R. Lyons and J. H. Lawrence. Decompression sickness; nature and incidence of symptoms during and after artificial decompression to 38,000 feet for ninety minutes with exercise during exposure. Aviation Med. J. 15:316-327 (Oct. 1944).

Bridge, E. V., F. M. Henry, O. L. Williams, and J. H. Lawrence. "Chokes": respiratory manifestation of aeroembolism in high altitude flying. Ann. Intern. Med. 22:398-407 (Mar. 1945).

Burkhart, T. M. Decreased tolerance to "bends." Hosp. Corps Quart. 18(5):38-43 (May 1945).

Burkhardt, W. L. Decompression sickness: factors (oxygen, exercise, and diet) which affect incidence of bends at altitude. J. A. M. A. 133:373-377 (8 Feb. 1947).

C

Capek, D. Characteristics of decompression sickness in aviators. Casop. Lek. Cesk. 92:758-766 (3 July 1953).

Carson, L. O. Critical evaluation of recent investigations of phenomenon of aeroembolism. US Marine Med. Bull. 40:284-290 (Apr. 1942).

Chaso, W. H. Anatomical and experimental observations on air embolism. Surg. Gynec. Obst. 59:569 (1934).

Chryssanthon, et al. Studies on dysbarism. II: Influence of bradykinin and bradykinin antagonists on decompression sickness in mice. Aerospace Med. 35:741-746 (Aug. 1961).

Clarke, R. W., et al. Peripheral circulation during decompression. OSRD Report No. 232 (29 Nov. 1943)

Clay, J. R. Pathology of experimental dysbarism. Presented at the thirty-fourth annual meeting of the Aerospace Medical Association, April 29 - May 2, 1963. In an attempt to simulate decompression sickness in man, several groups of investigators at the USAF School of Aerospace Medicine are producing dysbarism in dogs. At the end of these experiments the dogs are autopsied and studied by routine

histopathologic methods. In general, the tissue changes were similar to those of fatal human decompression sickness. Findings included multiple fat emboli in lungs, scattered petechiae, pulmonary congestion, and edema. Bone marrow and other tissue emboli were found in the pulmonary arteries in one-third of the animals. This is the first instance in which bone marrow emboli have been found in the absence of trauma of the bones. Fat emboli were also found in the renal glomeruli even in the absence of defects in the heart. Possible mechanisms for these findings are discussed.

Clay, J. R. Histopathology of experimental decompression sickness. Aerospace Med. 34(12):1107-1112 (Dec. 1963). Dogs overcompressed to 75 psi then decompressed to 10,000 or 15,000 feet simulated altitude (approximately 8 psi) developed pathologic changes similar to those seen in human decompression sickness. In addition, bone marrow emboli were produced in a fairly high percentage of the animals. Pulmanory fat embolization was massive in many instances, and the intravascular fat remained after five days. Other histopathologic changes are described.

Close, P. Effect of certain variations in the physiologic state of tolerance to explosive decompression. Naval School of Aviation Med., Report No., 1 Pensacola, Fla. (1 Dec. 1961). Administration in rats of norepinephrine, which raises blood pressure, decreases tolerance to explosive decompression. Perivascular hemorrhages were observed in all fatal decompressions. Lethal doses of norepinephrine indicate a histopathology remarkably similar to that found in explosive decompression. Explosive decompression in association with hypoxic hypoxia or the administration of histamine produces marked hemorrhagic consolidation which is typical of uncomplicated explosive decompression damage. On the basis of the above and other pertinent facts, major damage in explosive decompression may result from stretching of pulmonary vessels in conjunction with a sudden increased blood pressure.

Coburn, K. R. Decompression collapse syndrome; report of a case with successful treatment by compression to a pressure in excess of one atmosphere. Aerospace Med. 33:1211-1214 (Oct. 1962).

Coburn, K. R. Decompression sickness; present status. J. Royal Naval Med. Service (London) 48(2):69-75 (1962). In spite of extensive research on decompression sickness, the precise

mechanism of bubble formation and pain production, as in bends, is still a question. The symptoms of decompression sickness vary and appear to be dependent upon bubble location. These symptoms are skin manifestation, bends, bone changes, chokes, staggers, and decompression collapse syndrome (rarely observed but representing a grave condition). Age and exercise at altitude are known to increase the susceptibility to decompression sickness, especially to bends. Many representative tables and figures are included.

Colonna, P. C., and E. O. Jones. Aeroembolism of bone marrow. Arch. Surg. (Chicago) 56:16 (1948).

Cook, S. F., and E. Strayman. Effect of decompression on human metabolism during and after exercise. Amer. J. Physiol. 144:637-642 (Oct. 1945).

Cook, S. F. The inhibition of animal metabolism under decompression. J. Aviation Med. 16:268 (1945).

Cook, S. F., O. L. Williams, W. R. Lyons, and J. H. Lawrence. Comparison of altitude and exercise with respect to decompression sickness. War Med. 6:182-187 (Sept. 1944).

Coone, H. W., et al. Decompression sickness. US Armed Forces Med. J. 6(12):1787-1799 (Dec. 1955). A case of fatal decompression sickness in an obese (250 lbs.) passenger in a T-33 jet plane is presented. The patient ascended to 26,000 feet cabin altitude in 20 minutes and to 29,000 feet in a 3-1/2 minute period. Expcsure at this altitude for 2 minutes coincided with incoherence, numbness, visual disturbance and loss of consciousness. Return to 10,000 feet within 5 minutes and landing within 20 minutes was accomplished after onset of symptoms. A clinico-pathological discussion of this case shows that bends were the cause of death. Cerebral and pulmonary pathology and visible vasomotor phenomena may result from vasovagal reflexes.

Cotes, J. E., and D. G. C. Gronow. Influence of age and weight upon the incidence of decompression sickness in personnel bends - tested at the Royal Air Force Institute of Aviation Medicine between 1943 and 1952. Flying Personnel Research Committee (U.K.) Report No. FRRC 795, TIP U69640 (June 1952). This report gives a reduction of records of 433 subjects (83 service men and 350 civilians) engaged on high flying duties. Subjects were tested in the decompression chamber at 37,000 feet for 1 hour, unless earlier descent was required by the

onset of symptoms. The incidence of bends, chokes, and syncope or other symptoms which necessitated descent is classified by age and weight (under standard weight or more than 14 lbs. over standard weight) of the subjects. The incidence of obligatory descent increased from 8 among subjects aged 18 to 24 years to 40 among subjects aged 35 to 47 years. Choke and syncope cases made up 40 percent of the descents in all age groups and the incidence increased from 7 in subjects under standard weight to 18 in subjects more than 14 lbs. over standard weight. All cases of chokes occurred in the over-weight group. These findings are discussed, and certain conclusions are drawn from them.

E

Enzel, G. L., et al. A migraine-like syndrome complicating decompression sickness. War Med. 5:304 (1949).

Enzel, G. L., et al. Scotomata, blurring of vision, and headache as complications of decompression sickness. National Research Council, Commission on Aviation Med., Report 127 (1943).

Ernsting, J., J. L. Gedge, and G. J. R. McHardy. Anoxia subsequent to rapid decompression. Flying Personnel Research Committe, Report No. 1141. Air Ministry (U.K.) (1960).

F

Ferris, E. B., and G. L. Enzel. Clinical nature of high altitude decompression sickness. In Fulton, J. F. (ed.). Caisson sickness, diver's bends, flier's bends, and related syndromes, pp. 35-37. Philadelphia: Saunders, 1951.

Fisher, J. H. Bone-marrow embolism. A. M. A. Arch. Path. 52:315 (1951). Bone marrow embolism occurs much more frequently than has been previously reported. In a survey of 96 unselected fracture cases, 19 cases (19. 8 percent) of bone marrow embolism of the pulmonary arteries were found. The emboli were few in any particular case and might have been easily overlooked. Apparently, emboli have been overlooked in the past, since they have obstructed so few pulmonary arteries that significant disturbances did not occur in the lungs. Of the 19 patients, 13 were males and six females; age varied from 7 to 86 years. There was no predilection for any particular part of the lungs. In the surveyed material, all the blocks of lung tissue included pleural surfaces and, therefore, were from peripheral parts of the lungs. Order of frequency was as follows: the right lower lobe, the right upper lobe, the left upper lobe, the left lower lobe, and the right middle lobe. The patients survived from a few minutes (almost

instantaneous death) to six days after the injuries were inflicted. In one patient, the skull alone was fractured, but in most of the patients multiple bones were fractured. The bones involved (in order of frequency) were the ribs, pelvis, vertebrae, tibia, fibula, skull, and sternum. The persons were generally subjected to very forceful violence in automobile accidents. The bone marrow emboli were bland and caused no reaction at the point of arrest. Bone marrow embolism was occasionally associated with fat embolism, but bone marrow embolism also occurred alone.

Fulton, J. F. Decompression sickness. Philadelphia: W. B. Saunders Co., 1951.

Fulton, J. F. Factors affecting incidence of "bends" at altitudes. Milit. Surgeon 94:199-200 (Apr. 1944).

G

Gelfan, S., L. F. Mims, and R. B. Livingston. Explosive decompression at high altitudes. Amer. J. Physiol. 162:37 (1950).

Goodman, M. W. The syndrome of decompression sickness in historical perspective. Naval Medical Research Lab., AD290-167, New London, Conn.

Gould, T. R. A review of the high-altitude selection test. J. Royal Naval Med. Service 49:93-96 (1963). A review of the Royal Naval High-Altitude Selection Test and a discussion of its use (1961-1962) are presented. Even though the predisposing factors of age and overweight are considered, it is still impossible to predict that any one subject is susceptible to decompression sickness. Although the problem still remains, the selection test helps to eliminate any subject who is likely to suffer from the more severe forms of decompression sickness at altitude.

Gray, J. S., S.C.F. Mahady, R. L. Masland, and H. S. Wigodsky. Studies on altitude decompression sickness: I. Symptomalology. Aviation Med. 333-342 (Oct. 1946). The various types of symptoms experienced during 2, 920 man-flights to altitudes of 35, 000 to 38, 000

feet (simulated in a pressure chamber) are classified and described. Data are presented on altitudes of relief during descent, the frequency of the various types of symptoms, degrees of intensity, duration, and time-distribution during exposure to altitude.

Gray, J. S., and R. L. Masland. Studies on altitudes decompression sickness. II. The effects of altitude and of exercise. Aviation Med. 17:483-485 (Oct. 1946). The incidence of altitude decompression sickness increases with the altitude of flight. Exercise at altitude increases markedly the incidence of symptoms at a given altitude and lowers the threshold altitude for the occurrence of severe decompression sickness from 32,000 to 23,000 feet.

Gray, J. S., S. C. F. Mahady, and R. L. Masland. Studies on altitude decompression sickness: III. The effects of denitrogenation. Aviation Med. 17:606-610 (Dec. 1946). Denitrogenation accomplished by breathing pure oxygen for periods as short as fifteen minutes at ground level before ascent markedly reduced the incidence of severe decompression sickness in aviation cadets exposed for two hours to a simulated altitude of 38,000 feet. When carried out at altitudes of 20,000 feet or less, the denitrogenation procedure retained its full effectiveness in preventing symptoms. Above these altitudes its

effectiveness decreased. Exercise during the period of denitrogenation at ground level did not prevent symptoms. Denitrogenation had very little effect upon the incidence of gas pains at altitude. Denitrogenation for one hour before ascent completely prevented severe symptoms of bends and chokes in cadets exposed for one-half hour at 45,000 feet.

Gray, J. S. Prevention of decompression sickness by denitrogenation Air Surgeon's Bull. 1(11):8-9 (Nov. 1944).

Grognot, P. A., and F. Violette. Anatomo-pathological lesions of the cerebral cortex and of the lungs of dogs subjected to explosive decompression (from 9,000 to 15,000 meters). Med. Aero. (Paris) 7(4):476-480 (1952). Dogs were subjected to explosive decompression at simulated altitudes of 9,000 to 15,000 meters and were then immediately recompressed to ground level. The animals withstood the procedure fairly well though some lost consciousness. The lung tissue and parts of the cerebral cortex of animals killed immediately after the experiments or several days later, were studied microscopically. Injuries to the lungs (torn interalveolar partitions and circulatory stasis) and brain (hyperchromatic cells and microhemorrhages) were relatively minor.

Guest, M. M. Incidence of bends during different periods of the day. Air Surgeon's Bull. 1(6):5 (June 1944).

K

Kovalenko, E. A. The gaseous composition of the bubbles formed in high-altitude tissue emphysema. Pat. Fiziol. Eksp. Ter. 5(4):26-29 (July-Aug. 1961). Twenty-three albino rats were rapidly decompressed (7 to 8 mm. Hg) in an altitude chamber and remained in the rarefied atmosphere for 60 to 70 seconds. Samples of the liberated gas were withdrawn subcutaneously after the tenth, twentieth, and fortieth second of decompression and micro-analyzed. Emphysemic tissue swelling regressed during return to normal atmospheric pressure. Three rats died of acute hypoxia and respiratory arrests; in others, anoxic symptoms disappeared within 10 to 15 minutes after recompression. During the first 10 seconds the subcutaneous bubbles were composed of 73.7-percent N_2, 10.62-percent CO_2, and 16-percent O_2. With advancing emphysema, CO_2 concentration in the subcutaneous bubbles increased while N_2 content dropped. Death ensued from anoxia rather than from the boiling of body fluids.

L

Lamphier, T. A., M. Spaulding, F. Boodro and J. A. Scholl. Decompression illness (aeroembolism). Industrial Med. Surg. 31:240 (June 1962). Decompression illness or aeroembolism is a disorder caused by a too rapid decrease in atmospheric pressure with gaseous desaturation of the body tissues resulting in differential pressure around liberated gas bubbles and an emboli. A discussion on some of the physiological processes involved.

Lay, M. F. Neurocirculatory collapse at high altitude. Nederlands Militai-Geneeskudig Tijdschritt (Gravenhage) 8(10):271-281 (1955). The syndrome of neurocirculatory collapse appearing at high altitudes is reviewed in regard to its symptomatology, etiology, treatment, and prophylaxis.

Leverett, S. D. Jr., H. L. Bitter, and R. G. McIver. Studies in decompression sickness: I. Circulatory and respiratory changes associated with decompression sickness in anesthetized dogs. Presented at thirty-fourth Annual Meeting of the Aerospace Medical Association, 1963: Abstract in Aerospace Med. 34(3):260 (1963).

Luft, U. W., and W. K. Noell. Anoxic survival time of cerebral activity in sudden decompression to high altitudes. Amer. J. Physiol. 171:745 (1952)

Luft, U. C., H. G. Clamann, and H. F. Adler. Alveolar gases in rapid decompression to high altitudes. J. Appl. Physiol. 2:37 (1949).

Lyle, C. B. Protection of rapidly decompressed rats by pharmacologic and physical means. Amer. J. Physiol. 201(5):759-761 (Nov. 1961). Decompression from an ambient pressure of 520 mm. Hg to 30 mm. Hg in 0.075 seconds was fatal for 72 percent of a group of rats. Treatment before decompression with drugs acting on the nervous system reduced fatalities to only 12 to 37 percent. Rats given a local anesthetic agent intraperitoneally prior to decompression survived. Subjects whose abdomens were tensily distended with intraperitoneal saline before decompression survived. In each experimental group, mortality was significantly correlated with increased lung weight. In rats, the sudden distention of gas-containing abdominal viscera may have indirect, perhaps reflex, effects which may be related to the development of pulmonary edema and to survival.

M

Malette, Wm. G. Dysbarism: a review of 35 cases with suggestion for therapy. Aerospace Med. 33:1132-1138 (19 Sept. 1962).

Masland, R. L. Injury of the central nervous system resulting from decompression to simulated high altitude. School of Aviation Med., Report 481-1 (Oct. 1946). A small number of neurological reactions have been observed during the course of altitude indoctrination of individuals undergoing flight training in the Army Air Force. The occurrence of these reactions in an altitude chamber has provided an initial opportunity to observe the chain of events which follows a bout of decompression sickness.

McElroy, W. D., A. H. Whitely, G. H. Warren, and E. N. Harvey. Bubble formation in animals: relative importance of carbon dioxide concentration and mechanical tension during muscle contraction. J. Cell. Comp. Physiol. 24:133-146 (Oct. 1944).

Motley, H. L., H. I. Chinn, and F. A. Odell. Bends. J. Aviation Med. 16:210-234 (Aug. 1945).

N

Niess, O. K., and R. B. Stonehill. Dysbarism: a jet age problem of all physicians. Diseases of the chest 44(2):121-125 (Aug. 1963). With increased utilization of commercial jet aircraft, the possibility increases for loss of cabin pressurization and subsequent high altitude exposure of occupants. Therefore, physicians should become familiar with the manifestations of altitude dysbarism. The effects of reduced barometric pressure result from gases trapped within the body cavities or the evolution of gases from the liquid phase within the tissues or body fluids. In general, trapped gases can be quite discomforting but not usually dangerous unless the pressures generated are sufficient (which rarely happens) to cause rupture of a hollow viscus. Re-establishment of a patent foramen between the cavity and the atmosphere will result in relief. However, the release of gaseous nitrogen from body fluids or fat tissues can be life-threatening. Since this condition is more apt to occur in older and obese individuals, a significant percentage of the flying public can be considered "dysbarism prone." Manifestations are bends (with extreme pains), chokes (with respiratory distress, substernal pain, and dry cough) and neurocirculatory collapse. When circulatory failure becomes evident, mortality

can be expected and intensive care is essential. Since neurocirculatory failure develops rapidly after a relatively symptom-free period, individuals who experience any manifestations of dysbarism should be observed for at least two hours after removal from altitude exposure. Treatment is supportive and includes oxygen administration. However, the early correction of reduced circulating plasma volume is essential.

Nims, L. F. Physical theory of decompression sickness. In Fulton, J. F. (ed.). Decompression sickness, diver's and flier's bends, and related syndromes, pp. 192-222. Philadelphia: Saunders, 1951.

O

Odland, L. T. Total decompression illness at an altitude of 22,000 feet. Aerospace Med. 30(11):840-846 (1959).

Rainsford, S. C. More recent additions to our knowledge of effects of compression and decompression on man: application to practical problems connected with high flying (including aeroembolism). J. Roy. Nav. Med. Service, Report No. 28:326-332 (Oct. 1942).

Rait, W. L. Post-decompression shock. Med. J. Australia, 2(15):533-534 (1952). Altitude flying may lead to collapse during decompression or after return to the ground. Studies of decompression sickness usually center around the formation of gas bubbles in the blood stream, but little has been done with regard to the mechanism of post-decompression shock. Clinical investigations suggest that in some subjects a trigger mechanism is set off during decompression. This mechanism starts the development of secondary shock which might be due to aeroembolism or biochemical disturbance (e.g., a disorder of nucleotide metabolism, acute adrenal cortical insufficiency, or a histamine upset). A study of these disturbances requires the following tests: determination of the plasma pentose content (any increase would indicate a disturbance of the nucleotide metabolism); estimation of the ascorbic acid content of the adrenal glands and an absolute lymphocyte count; and determination

of the histamine and the histaminase content of the lungs after decompression. Primary and delayed reactions should be carefully observed as the prognosis of shock depends upon restoration of the blood pressure. Pilots should be examined before and after flight.

Rappaport, H., M. Raum and J. B. Horreil. Bone marrow embolism Amer. J. Path. 27:407 (1951).

Robie, R. R., F. W. Lovell, and F. M. Townsend. Pathological findings in cases of decompression sickness. Aerospace Med. 31:885 (1960).

Rodhard, S. Recurrence of decompression sickness on reascent to high altitudes. Proc. Amer. Soc. Exp. Biol. 4:59 (1945).

Romano, V., et al. Migraine-like syndrome complicating decompression sickness: clinical and electroencephalographic observations. Trans. Amer. Neurol. Ass. 0:60-64 (1944).

Romano, J., et al. Syncopal reactions during simulated exposure to high altitude in decompression chamber. War. Med. 4:475-489 (Nov. 1943).

Roxburgh, H. L. Decompression sickness. Med. Press 229(8):174-178 (1952). The development time of symptoms in decompression sickness varies with the individual but is known to increase rapidly at altitudes over 25,000 feet. The symptoms include "bends," hypersensitivity of the skin, "chokes," abdominal distention, visual disturbance, and collapse. The onset of decompression sickness is affected by such factors as body type, amount of pre-exercise, temperature, oxygen supply, rate of ascent, altitude, and duration of exposure to altitude. The prevention of decompression sickness may be effected by adequate pressurization and denitrogenation before flight.

S

Schaefer, K. E., W. McNulty and C. Carey. Development of air embolism Abstract in Fed. Proc. 16 (1^{I}):113 (Mar. 1957). Dogs (with the trachea closed) were decompressed within 2 minutes. The pressure gradient between intratracheal and intrapleural pressure (transpulmonic pressure) was found to be the decisive factor in producing air embolism. The critical level of transpulmonic pressure was 60 to 70 mm. Hg. When binders were placed around the chest and abdomen, distention of the lungs was prevented and transpulmonic pressure was kept from reaching a critical value. Abdominal binders failed to give protection against air embolism. In every case of air embolism, bubbles were found in the carotid artery bubble trap. A transient circulatory failure (all circulatory pressures in the pulmonary as well as in the systemic circulation approaching the same level, with simultaneous disappearance of pulse pressure) occurred whether or not air embolism developed, and was, therefore, not the cause of air embolism.

Schilling, J. A., and R. B. Harvey. Effect of simulated altitude and explosive decompression on dogs with bilateral partial pulmonary resection. Fed. Proc. 13(11):129 1954. These experiments tried

to determine the tolerance of unanesthetized dogs to acute exposure to varying simulated altitudes and to explosive decompression following resection of two or more lobes of each lung. Healthy mongrel dogs were selected. Hematocrits were checked initially and throughout the experiments and normal cardiac function was assumed. The altitude tolerance of the normal animals was tested by ascent to 33,000 feet (altitude chamber), using the EEG and the ability of the dog to stand as a criterion of hypoxia. Exercise was carried out on a treadmill with measure of oxygen consumption and calculation of maximal pulmonary diffusion. Arterial oxygen tension after exercise was checked. Following initial training on the treadmill and control studies, the middle and lower lobes of the right lung were resected and a suitable recovery period allowed. The experiments were repeated and the upper lobe and the lingular segment of the left lung were resected. The experiments were again repeated, and the animal was sacrificed after measurement of functional residual volume by rapid decompression. Initial results indicate that the dogs tolerated acute exposure to altitude remarkably well following resection of two to four of the seven major lobes or both lungs.

Shust, V. Decompression changes in the blood. Fiziol. Thur. SSSR 46(5):618-622 (1960).

Smedal, H. A., E. B. Brown and C. E. Hoffman. Incidence of "bends" pain in a short exposure to simulated altitudes of 26,000, 28,000 and 30,000 feet. Aviation Med. 17:67-69 (Feb. 1946). A total of 1,731 flight students were exposed to altitudes of 26,000, 28,000 and 30,000 feet for twenty minutes at either room or very low temperature with approximately one-half of the subjects in each flight exercising at three-minute intervals. Among exercising subjects, higher incidence of "bends" pains occurred under warm conditions at all three altitudes. Among resting subjects, exercise markedly increased the incidence of bends. "Bends" pain occurred in exercising flight students in a twenty-minute exposure at simulated altitudes as low as 26,000 feet. In a small percentage of cases, "bends" pain was severe enough to require descent.

Suzan, O. Electroencephalogram in syncopal reactions collapse at 18,000 feet simulated altitude in low pressure chamber. War Med. 8:9-15 (1945).

Sweeney, H. M. Explosive decompression. Air Surgeon's Bull. 1:1-10 (1944).

V

Vozza, R. Opthalmological aspects of the decompression syndrome with special regard to explosive decompression. Riv. Med. Aero. (Roma) 20(3):543-558 (July-Sept. 1957).

Whitehorn, W. V., A. Lein, and F. A. Hitchcock. The effects of binding of the abdomen and thorax on pulmonary lesions produced by explosive decompressions. J. Aviation Med. 18:102 (1947).

Whitehorn, W. V., A Lein, and A. Edelmann. The general tolerance and cardiovascular responses of animals to explosive decompression. Amer. J. Physiol. 147:289 (1946).

Wilson, C. L. Production of gas in tissue at low pressures. School of Aerospace Med., AD 268 376, Brooks AFB, Texas. The development of a gas phase in human tissue was studied by exposing the left hands of 6 volunteer subjects to a total pressure of 49 mm. Hg or less. Gas pockets which developed in the hands of four subjects were clearly discernible by visual inspection and an appropriate roentgenographic technique. The gas pocket developed at chamber pressures less than 26 mm. Hg. (23.2 km.) on initial exposure and disappeared at a chamber pressure greater than 226 mm. Hg (9.2 km.). The swelling was never painful, always disappeared promptly on repressurization of the chamber, and has never caused any apparent temporary or permanent injury to the hand. Subsequent

exposure of the hand to a low total pressure caused swelling at 70 mm. Hg or more. Carbon dioxide and water are believed to be the main gases involved in the phenomenon.

Wilson, J. W., and E. Comfort. Anoxia following explosive decompression from altitudes below 10,000 feet. Mem. Rep. Aero. Med. Lab. MCREXD-696-111A: 1-10 (10 May 1948).

AUTHORS UNKNOWN

Aeroembolism induced by exercise in cadets at 23,000 feet. School of Aviation Med. Randolph Field, Texas. (26 Jan. 1944).

Chamber reactions. U.S. Air Force Med. Service 6(11):21-22 (Nov. (Nov. 1955). The neurocirculatory collapse is an untoward physiological reaction rarely occurring during ascent to simulated altitude. In neurocirculatory collapse, symptoms of dysbarism usually precede the maximum circulatory or neurological changes which may or may not be accompanied by loss of consciousness. It should not be confused with collapse due to hypoxia, hyperventilation, excessive positive-pressure breathing, or apprehension. The etiology of neurocirculatory collapse is unknown. All cases of neurocirculatory collapse are to be considered dangerous. Individuals showing signs of decompression sickness, neurological changes, circulatory changes, or any unusual symptoms should be recompressed to ground level as rapidly as possible, watched for two hours, and hospitalized if there are any residual symptoms. Any unusual symptoms should be reported to the flight surgeon for immediate action to prevent the development of serious reaction. Prophylaxis is the preferred treatment.

IV, HYPERCAPNIA

A

Altschule, M.D., and W.M. Sulzbach. Tolerance of the human heart to acidosis: reversible changes in RS-T intervals during severe acidosis caused by administration of carbon dioxide. Amer. Heart J. 33:458-463 (1947).

Arends, R.L., C.J. Rayburn, W.B. Draper, and R.W. Whitehead. Effect of diffusion respiration and of inhalation of high concentrations of CO_2 on plasma volume, thiocyanate space, blood cells, and O_2 capacity. Amer. J. Physiol. 171 (2):507-512 (1952). The term "diffusion respiration" has been applied to a physiological process by means of which mammals in respiratory arrest are able, without the aid of artificial respiration, to secure sufficient O_2 from the ambient atmosphere to maintain life as long as an hour and a half. The phenomenon is seen only when the following conditions are fulfilled: replacement of nearly all the N_2 of the ambient atmosphere, respiratory passages, blood, and tissue with O_2; adequate circulation; and patent airways. The disturbances in plasma volume, thiocyanate space, and cellular components of the blood during diffusion respiration

and inhalation of O_2 or of mixtures of 20- or 40-percent CO_2 in O_2 have been investigated in the dog. Severe hypercapnia, whether brought about by diffusion respiration or by inhalation of CO_2 in O_2, results in a marked decrease in plasma volume, an irregular increase in extracellular fluid (thiocyante space), substantial increase in red cell count and volume, and O_2 capacity of venous blood. There is no consistent change in either the white or differential count.

Areskag, N.H. The influence of hypercapnia and hypocapnia on the heart-lung preparation of the dog. Acta Soc. Med. Upsalienis 67 (3/4):135-142 (1962). A study was made of acid-base balance at the switching over from the intact animal to heart-lung preparation (HLP) with unchanged preliminary ventilation. A study was also made of changes of pH to ascertain whether they provoked changes in the electroloyte balance of the HLP system and changes in the different functional parameters (arterial pressure, venous pressure, and heart rate). The pH variations were produced by pCO_2 variations in the inspired gas mixture. All HLP's were metabolically acidotic, compared with the normal human buffer line, independently of hypercapnia or hypocapnia. In the late stages, an increasing metabolic acidoses appeared. Hypocapnia gave a lower degree of hypodynamia than

normocapnia and hypercapnia. Sudden increases of the CO_2 content of the inspired air often produced acute myocardial failure. With hypercapnia, there was a tendency for a higher K loss from the myocardial cell than with hypocapnia and normocapnia. No changes in Na concentration were found. A major metabolic influence on plasma pH was apparent only in the terminal stage of myocardial failure, while at other times the pH was mainly dependent on respiratory factors. In general, sudden variations of O_2 or CO_2 content of the inspired air were most effective in causing a change of HLP function. Such variations produced severe disturbances in the heart rhythm. This may be due to changes in the intracellular ionic milieu of the myocardium. In contrast the HLP appears to have a good adaptability to fairly wide variations in plasma pH, provided that such variations take place slowly.

Aström, A. On the action of combined carbon dioxide excess and oxygen difficiency in the regulation of breathing. Acta Physiol. Scand. 27, (98):1-61 (1952).

B

Baran, C., and B. Lewalski. Pulmonary ventilation in rats in hypoxic-hypercapnic hypothermia. Acta Physiol Pol. 8(3-3a): 280-381 (1957). Deep hypothermia (14 to 15°C.) decreased the respiratory frequency (10 to 25 per minute) in normal rats. With increasing temperature (19 to 20°C.), the respiratory frequency became 100 per minute. At further warming, the respiratory frequency rose to 165 per minute and ventilation increased. Urethane anesthesia or intraperitoneal administration increased the frequency and decreased pulmonary ventilation.

Barker, E.S., R.B. Singer, J.R. Elkenton, and J.K. Clark. The renal response in man to acute experimental respiratory alkalosis and acidosis. J. Clin. Invest. 34:515 (1957).

Barnet, T.B., and R.M. Peters. The ventilatory response to carbon dioxide and to oxygen after acclimatization to carbon dioxide. AD293-993. A chamber has been designed so that dogs can be exposed for prolonged periods to abnormal atmospheres. The concentrations of CO_2 and O_2 are continuously controlled and recorded. Exposure of dogs to approximately 3-percent CO_2 in air for 6 days or more resulted in a decrease in the ventilatory response to CO_2. In control dogs the breathing of

50-percent O_2 for 30 minutes was associated with a slight-to-moderate increase in ventilation without a significant change in arterial pCO_2. After acclimatization to CO_2 oxygen breathing was associated with little change in ventilation but with a rise in arterial pCO_2.

Bleich, H.L., P.M. Berkman, and W.B. Schwarts. The response of cerebrospinal fluid composition to sustained hypercapnia. J. Clin. Invest. 43:11-16 (Jan. 1964). Cerebrospinal fluid (CSF) and plasma pH, CO_2, bicarbonate, and electrolytes were measured in dogs exposed at 1 and 1/2-percent CO_2 for 1/2, 3, 8, or 24 hours or 5 days. CSF bicarbonate rose gradually during the first 8 hours of exposure remaining at the same level during the next 4 days. Plasma water bicarbonate was increased after 1/2 hour, and showed no further significant increase until a measurement was made after 5 days. Plasma bicarbonate was higher than CSF bicarbonate after 1/2 hour, lower after 24 hours, and the same after 5 days. Hydrogen ion concentration in both fluids were increased to a maximum during the first 1/2 hour of hypercapnia and decreased slightly thereafter. Plasma and CSF chloride was decreased after 5 days by an amount equivalent to the rise in bicarbonate concentration. Sodium and potassium concentrations were not significantly changed. The CSF-plasma ratios of all

electrolytes were the same after prolonged hypercapnia as in controls, suggesting that any existing potentials governing ion distribution in the two fluids were maintained during hypercapnia.

Blinova, A. M. The effects of reflexes upon the brain's blood supply (2nd Report). Interoceptive small intestine irritation in hypercapnia affecting the brain blood supply. Biul. Eksp. Biol. Med. 43 (3):3-7 (1957). In dogs, the blood supply of the brain, estimated by the volumetric speed of the blood stream in the meninx, was investigated by the thermoelectric method. The small intestinal interoceptors were irritated by dilating them with air under normal conditions and in short-lasting hypercapnia (H). In H conditions, interoceptor irritation resulted in a greater intensity of the blood stream than when room air was inhaled. The reaction was reversed 20 to 40 seconds after termination of H, and previous conditions were restored in 60 to 90 minutes.

Bottoni, A. Effects of hypercapnia on retinal arterial pressure. Ann. Oculist. (Paris) 194 (4): 320-327. (Apr. 1961). A constant increase in retinal arterial blood pressure was found in subjects

breathing a mixture of air containing 5 percent CO_2. This phenomenon was possibly due to the vasodilatory effect of CO_2 on the cerebral and retinal blood vessels.

Bowman, M.J. Clearing the air. J. Brit. Interplanetary Soc. (London) 14(5):291-293 (Sept-Oct. 1955). The author discusses and rejects J.B.S. Haldane's value of 3 percent (see item no. 4296) as the maximum permissible concentration of CO_2 in space cabin atmosphere. In view of the incomplete knowledge of the processes of acclimatization of such concentration of CO_2, there is a possibility of harmful consequences of changes in respiration, blood, and kidney functions and excretion in response to CO_2. The minimum sodium chloride requirement for the human organism is more flexible depending upon activity level, environmental conditions, and time period. Contradictory references are cited in respect to the use of lithium compounds for CO_2 absorption in the cabin atmosphere.

Brazier, M.A.B. Physiological effects of carbon dioxide on the central nervous system in man. Medicine 22:205-221 (1943).

Broom, B. Effects of 20-percent carbon dioxide in oxygen on the body temperature of the rat during surface cooling. Nature (London) 193:1262-3 (31 Mar. 1962).

Brown, E. B., Jr., and A. Morvlem. Potassium loss from the heart during the immediate post-hypercapnic period. Amer. J. Physiol. 198(5):962-964 (1960). Experiments have been carried out on mongrel dogs in which plasma potassium concentrations in blood samples simultaneously drawn from the aorta and coronary sinus have been determined before, during, and following 4 hours of high CO_2 breathing. No significant difference between potassium concentrations in aorta and coronary sinus blood was evident before or during breathing of high CO_2 mixtures. Five minutes after returning to air breathing, however, coronary sinus plasma potassium concentration was significantly elevated above that of the aorta. This loss of potassium from the heart is accompanied by severe cardiac irregularities: premature systoles, ventricular tachycardia, and, sometimes, ventricular fibrillations. Coronary blood oxygen concentration differences decrease significantly during hypercapnia, and estimates by the N_2O technique indicate that this decrease is the result of an increase in coronary flow.

Brown, E. B. Plasma potassium changes produced by inhalation of 30- and 40-percent carbon dioxide in the dog. Fed. Proc 14(11):(21 Mar. 1955). Anesthetized dogs were exposed to atmospheres of 30-percent CO_2 in oxygen for two hours followed by 40-percent CO_2 in oxygen for two hours exhibited gradual increases in plasma potassium concentrations from a mean of 4. 1 mEq. /l. at 15 min. to a mean of 5. 6 mEq. /l. at 2 hours with a high level persisting thereafter. During the first 5 minutes after return to air breathing, a further rise was noted, followed by a gradual decline.

Brown, E. B. Role of hyperkalemia in production of ventricular fibrillation following hypercapnia. Proc. Soc. Exper. Biol. Med. 90(2):319-323 (Mar 1955). The plasma potassium of dogs increased gradually during the breathing of 30- and 40-percent CO_2 in O_2 for four hours, and increased more sharply to a maximum of 8. 2mM. /l. during the first 5 minutes of return to air breathing and gradually decreasing thereafter. Two of the 13 dogs in the group died in ventricular fibrillation after return to air breathing. When KCl was administered by intravenous drips during CO_2 or air breathing, levels of 12. 96-14. 39mM. K/l. were reached before cardiac arrest or ventricular fibrillation occurred. Thus the potassium increase normally occurring during hypercapnia was not sufficient alone to produce cardiac arrest.

To test the role of a rapid fall in CO_2 tension and rise in pH in cardiac arrest, dogs were hyperventilated with 100 percent O_2 after the plasma potassium level normally occurring during extended CO_2 breathing (8 to 9 mM. /l.) was thought to have been reached by KCl administration during 30 minutes of hypercapnia. Cardiac arrest or fibrillation was observed in these animals at a potassium level of as low as 8.4 mM. /l. Previously it had been found that return to air breathing after 30 minutes of high CO_2 breathing, with potassium presumably remaining at a low level, did not produce arrest or fibrillation. Thus it appears that while neither a hypercapnic increase in plasma potassium nor a rapid fall in CO_2 tension is sufficient alone to produce cardiac arrest or fibrillation, the two in combination are responsible for the cardiac damage occurring during hypercapnia.

Brown, E. B., and F. Miller. Ventricular fibrillation following a rapid fall in alveolar carbon dioxide concentration. Amer. J. Physiol. 169(1):56-60(1952). Ventricular fibrillation and deaths have been produced in 11 of 15 dogs by a rapid reduction in alveolar carbon dioxide tension following 4 hours of breathing 30- to 40-percent carbon dioxide in oxygen. Cardiac arrhythmias appeared in the 4 dogs that survived the procedure. Two dogs subjected to the same high carbon

dioxide for the same length of time showed no cardiac arrhythmias and survived the procedure when the alveolar carbon dioxide tension was reduced slowly.

Brown, E. W. The physiological effects of high concentrations of carbon dioxide. U.S. Marine Med. Bull. 28:721-734 (1930).

C

Chapin, J. L. Evidence for simultaneous lowering of upper and lower limits of CO_2 tolerance. Abstract in Fed. Proc. 15(11):34 (Mar. 1956). Nine subjects resided continuously at high altitude (Mt. Evans, Colo. 14, 150 and Echo Lake 10,600 feet) for three weeks, during which the upper-limits tolerance was measured by ventilatory response to gradually increasing CO_2 in a rebreathing system. Their CO_2 tolerances measured by a performance test and by the appearance of tetany, both during articially induced hyperventilation. At the end of the 3-week acclimatization period, the subjects returned to Denver, Colo., elevation 5,300 feet for recovery measurements and the establishment of normal values. Exposure to the altitude of Mt. Evans and Echo Lake resulted, in addition to the well known sensitivity to high CO_2, in performance improvement during and almost complete absence of the symptoms of tetany at those CO_2 levels which had produced tingling and twitching during the control period. These results are interpreted as indicating that with low CO_2 acclimatization the CO_2 range moves down rather than merely shortening.

Chapin, J. L., A. B. Otis and H. Rahn. Changes in sensitivity of the respiratory center in man after prolonged exposure to 3 percent CO_2. Wright Air Development Center Tech. Rept. No. 55-357:250, Wright-Patterson AFB, Ohio (1955).

Clancy, R. L., and E. B. Brown, Jr. Changes in bone potassium in response to hypercapnia. Amer. J. Physiol 204(4):757-760 (1963). Experiments were carried out on two groups of rats and one group of dogs for the purpose of determining the effect of hypercapnia on bone potassium. Rats that breathed 30-percent CO_2 for 4 hours did not show a statistically significant change in the concentration of potassium in c.. act bone. Four hours of dogs' breathing 30-percent CO_2 and 48 hours of rats' breathing 15-percent CO_2, however, resulted in an increase in bone potassium. Changes in potassium in bone and interstitial fluid were in the same direction but the magnitude of changes in interstitial fluid was not sufficient to account for the change in bone. All of the experiments indicate that bone does not contribute to the hyperkalemia with respiratory acidosis, since bone apparently takes up potassium that is being transferred to the extracellular fluid from other sources.

Consolayis, W.V., et al. Effects on man of high concentrations of carbon dioxide in relation to various oxygen pressures during exposures as long as 72 hours. Amer. J. Physiol. 151:479-503 (1947).

Cunningham, D.J.C., B.B. Lloyd, and C.C. Michel. Acid-base changes in the blood during hypercapnia and hypocapnia in normal man. In proceedings of the Physiological Society, 15-16 Dec. 1961. It seems to be widely assumed that during the short-term inhalation of CO_2-air mixtures, the acid-base changes occurring in the plasma follow the in vitro CO_2 dissociation curve, and early experiments appeared to confirm this (Douglas and Havard, 1963; Shock and Hasting, 1935). We have found in 11 out of 13 experiments on 9 subjects that the pH-(HCO_3-) relations during the inhalation of 5- to 6-percent CO_2 diverge from those predicted by the in vitro curve of the resting blood of the subject in the direction of a small (about 1 mEq./l.) metabolic acidemia. The time course of the divergence was approximately exponential. The half time was dependent on the magnitude of the imposed change of alveolar pCO_2, being 8-9 min. for a rise of 3-6 mm.Hg and 2-3 min for a rise of 7 to 12 mm. Hg. Eight experiments on the blood were also made after lowering the inspired CO_2 to 2 percent, and in 7 of these some degree of metabolic acidemia was present after 30 minutes.

Cutler, R.G., F. Ulvedal, J.E. Herlocker, and B.E. Welch. Human tolerance for carbon dioxide in nitrogen atmosphere. Presented at Thirty-Fourth Annual Meeting of the Aerospace Medical Association, Los Angeles, 29 Apr. - 2 May 1963.

Cutler, R.G., et al. Human response to carbon dioxide in the low-pressure, oxygen-rich atmosphere. Aerospace Med. 35 (4):317-323 (no date). Eight subjects were successively exposed to an inspired carbon dioxide partial pressure of 21mm. Hg (equivalent to 3 percent at sea level), in an atmosphere of 700 mm. Hg total pressure and in an oxygen atmosphere of 20 mm. Hg total pressure. The duration of exposure to carbon dioxide was 4 days in each case. Response to carbon dioxide was nearly the same at the two different pressures as measured by the degree of hyperventilation and hypercapnia produced. Respiratory acidosis reached a maximum after a 2-day CO_2 exposure at each pressure and was followed by a pH shift on the third and fourth days due to renal or metabolic consumption. There was no objective evidence in the respiratory studies of an adaptive acclimatization to carbon dioxide during the 4-day exposures. The subjective ability to

detect carbon dioxide in the atmosphere was not always reliable, especially after prolonged exposure. No performance deterioration was measured, and, in fact, operator efficiency was maintained on a remarkably even keel.

D

Davis, H. W., G. R. Brow, and C. A. L. Binger. Respiratory response to carbon dioxide. J. Exper. Med. 41:37-51 (1925).

Dejours, P., Y. Labrousse, J. Raynaud, and R. Flandrois. Studies on carbon dioxide studies of ventilation in man. J. Physiol. (Paris) 50(2):239-243 (Mar. 1958).

Dripps, R. D., and J. H. Comroe. The respiratory and circulatory response of normal man to inhalation of 7.6- and 10.4-percent CO_2 with a comparison of the maximal ventilation produced by severe muscular exercise, inhalation of CO_2, and maximal voluntary hyperventilation. Amer. J. Physiol. 149:43-51 (1947).

E

Eldredge, F., and J.M. Davis. Effect of mechanical factors on respiratory work and ventilatory responses to CO_2. J. Appl. Physiol. 14:721 (1959).

F

Fe[illegible]al, K.A., M.A. [illegible]ner, and A.B. Dubois. Comparison between the time available and the time required for CO_2 equilibration in the lung. J. Clin. Invest. 42:24-28 (Jan. 1963).

Fishman, A.P., H.W. Fritts, and A. Cournand. Effects of breathing carbon dioxide upon the pulmonary circulation. Circulation 22(2):220-225 (1960). The effects of inhaling 5-percent CO_2 in air on the pulmonary arterial blood pressure and flow were studied in 5 subjects with normal pulmonary circulations and in 10 patients with chronic pulmonary emphysema. In the five control subjects, with an average increase in arterial PCO_2 of 6 mm. Hg (37 to 43) and a 3-fold increase in minute ventilation, both pulmonary arterial blood pressure and flow remained unchanged. In the 10 patients with chronic pulmonary emphysema with a similar increase in arterial PCO_2 (45 to 52) and a 2-fold increase in minute ventilation, there was a 14 percent increase in cardiac output and a rise in pulmonary arterial mean pressure of 4 mm. Hg. In these patients, an increment in pulmonary arterial pressure was invariably associated with an appreciable increment in blood flow. The present study affords no

support for the view that the breathing of air enriched with CO_2 elicits pulmonary vasoconstriction in either normal subject or in patient with chronic pulmonary disease.

G

Gellhorn, E., and H.F.Hailman. Parallelism in changes of sensory function and electroencephalogram in anoxia and effect of hypercapnia under these conditions. Psychosomat. Med. 6:23-30 (1944).

Gellhorn, E., and S.H. Kraines. Word associations as affected by deficient oxygen, excess of carbon dioxide, and hyperpnea. Arch. Neurol. Psychiat. 38:491-504 (1937).

Gellhorn, E. Influence of carbon dioxide in combating effect of oxygen deficiency on psychic processes. Amer. J. Psychiat. 93:1413-1434 (1937).

Gellhorn, E. The effect of O_2-lack, variations in the CO_2-content of the inspired air, and hyperpnea on visual intensity discrimination. Amer. J. Physiol. 115:679-684 (1936).

Gellhorn, E., and I.F. Spiesman. Influence of variations of oxygen and carbon dioxide tensions in inspired air upon hearing. Proc. Soc. Exper. Biol. Med. 32:47-48 (1934-1935).

Gibbs, F.A., E.L. Gibbs, W.G. Lennox, and L.F. Nims. The value of carbon dioxide in counteracting the effects of low oxygen. J. Aviation Med. 14:250-261 (1934).

Gibbs, E.L., F.A. Gibbs, W,G. Lennox, and L.F. Nims. Regulation of cerebral carbon dioxide. Arch. Neurol Psychiat. 47:879-889 (1942).

Gibbs, F.A., S. Williams and E.L. Gibbs. Modifications of the cortical frequency spectrum by changes in CO_2, blood sugar, and O_2. J. Neurophysiol 3:49-58 (1940).

Gray, J.S. Concerning the use of carbon dioxide to counteract anoxia. AF School of Aviation Med., Project No. 310, Report No. 1, Randolph AFB, Texas (26 Aug. 1944).

H

Haldane, J.B.S. Clearing the air. Jour. Brit. Interplanetary Soc. (London) 14(5):293-295 (Sept.-Oct., 1955). The author defends 3 percent CO_2 per volume in the air as a harmless concentration for the space-cabin atmosphere. Man at rest has approximately 6 percent CO_2 in the alveolar air. This level is maintained by regulating the volume of air breathed per minute. As the CO_2 level in the inspired air is increased, the volume per minute increases. Changes in blood and kidney function are viewed as compensatory reactions. Inactivity and a short time of exposure further reduce the possibility of any ill effects for the astronaut.

Haldane, J.B.S. The purification of air during space travel. J.Brit. Interplanetary Soc. (London) 14(2):87-89 (Mar.-Apr, 1955). The value of 0.3 percent CO_2 per volume of air is disputed as the maximum permissible concentration in the atmosphere of a space cabin. The author maintains that a 3 percent CO_2 concentration is physiologically acceptable and permits a more efficient utilization of the absorbent. He cites his own experiences as a subject in tests of the submarine atmosphere, where a 48-hour stay in an atmosphere with up to 3 percent CO_2 concentration did not have any ill effects.

Hall, F.G. The role of carbon dioxide in altitude tolerance. AD 23-807 (1953). When man breathes ambient air at high altitudes, a hypoxic stimulus causes a rapid increase in breathing. This leads to an abnormal loss of carbon dioxide from his blood. When carbon dioxide is added to the inspired air, a still greater increase in breathing occurs. This demonstrates that the two stimuli to breathing are additive in their effect. When carbon dioxide is added to inspired air of subjects breathing ambient air at altitude, the time of consciousness is increased. This i due mainly to the increased supply of oxygen to the blood by virtue of increased lung ventilation. The hypoxic and carbon dioxide stimuli to breathing act independently at altitude. When both are strong they act additively. When, however, the partial pressure of oxygen in the lungs falls below a certain level, the hypoxic stimulus alone regulates breathing. Adding carbon dioxide to oxygen breathed by men at altitude seems to increase the elimination of nitrogen from their bodies appreciably.

Hastings, B.K., and K.E. Schaefer. The effects of prolonged exposure to elevated concentrations of carbon dioxide on respirations, alveolar carbon dioxide tension, and lung volume. Naval Medical Research

Lab., AD 272 423, New London, Conn. Twenty-three subjects were exposed to an atmosphere consisting of 1.5-percent carbon dioxide in 21-percent oxygen for a period of 42 days. Respiratory studies were carried out on two groups of 10 subjects each through the experiment, which had the following results: the respiratory minute volume of these subjects and their alveolar carbon dioxide tensions were increased; there was no significant change in vital capacity, inspiratory and expiratory reserve, or tidal volume; the carbon dioxide excretion in the expired air and in the urine showed a parallel pattern, that is, an initial drop during the first eight days, followed by a rise during the next two weeks until approximately normal levels are reached. Subjects were classified into two groups: those with a low and those with a high ventilatory response to 15 minutes exposure to 5-percent CO_2. The ventilatory response to 5-percent CO_2 was found significantly reduced in the high ventilation group at the end of exposure to 1.5-percent CO_2, while no such change could be observed in the low ventilation group - with a respiratory pattern different from the high ventilatory group.

Hawkins, W.R., G.T. Hautz, and G.R. Shenkamp. Heat load and CO_2 during simulated space flight. In preprint of annual meeting of Aero Medical Association, Los Angeles, 27-29 April, 1959. After a careful preflight examination and indoctrination, one subject underwent three simulated space-cabin flights of 48 hours duration each and 30 days apart. Each flight was conducted at one-half atmosphere or 380 mm. Hg pressure in which the cabin oxygen was automatically maintained at 150 mm. Hg pressure. The work program was the same for any 24-hour period. The only changes in the flight profile involved the carbon dioxide concentration to which the subject was subjected, his diet, and the heat load as generated by the wearing of a partial pressure suit. During the first flight, the subject was required to wear a partial pressure suit throughout the flight and his diet had a low acceptance rating. The carbon dioxide concentration was allowed to build up gradually over the first 18 hours, reaching a maximum concentration of 38 mm. Hg pressure. This concentration was maintained for 2 hours and then absorbed. The second 24-hour period was characterized by constant absorption of the carbon dioxide until the eighteenth hour, at which time there was a rapid build-up of carbon dioxide, exposing the subject to a maximum concentration of 38 mm.

Hg pressure for 2 hours. The flight profile for the second 48-hour flight was the same except that the partial pressure suit was not worn, thus reducing the heat load. The third and final flight was made under more or less optimum conditions, that is, the carbon dioxide was constantly absorbed throughout the entire flight; a comfortable "shirt-sleeve" attire was worn and the poor acceptance diet was replaced by foods which the subject liked.

Hill, J. L., E. K. Jenkins, and M. J. Tuttle. The respiratory response to inhalation of 7-percent carbon dioxide: further observations. Med. Serv. J. Canada, 18:19-28 (19 Jan. 1962).

Hill, L., and M. Flack. The effects of excess of CO_2 and want of O_2 on the respiration and circulation. J. Physiol. (London) 37:77-111 (1908).

Himwich, H., et al. Effects of adding carbon dioxide to oxygen enriched atmospheres in low pressure chambers: the oxygen and carbon dioxide tensions of cerebral blood. J. Aviation Med. 13:177 (1942).

Honda, Y., N. Hasumura, T. Matsui, and K. Nakanium. Threshold CO_2 dependence on arterial pH for the respiratory system of dogs. J. Appl. Physiol. 17:866-870 (Nov. 1962).

Ivanov, Y. N. Change in the bioelectrical activity of various brain regions of cats and dogs on exposure to carbon dioxide. Foreign Tech. Div., Air Force Systems Command, AD 277650, Wright Patterson Air Force Base, Ohio. Inspiration of carbon dioxide in small (to 5 percent) concentrations leads to the development of characteristic electrical reactions in all regions of the brain of cats and dogs: desynchronization in the cerebral cortex and regions of the optic thalami; desynchronization and appearance of slow waves or changes in the discharges of electrical impulses in the medulla oblongata. The electrical activity of the cerebral cortex, and mainly of its frontal regions, changes earliest on exposure to small concentrations of CO_2. The exposure of appreciable concentrations of CO_2 (8-10 percent and higher) and of pure CO_2 does not make it possible to ascertain the characteristics of the electrical responses of the brain region and the normal dynamics of their occurrence. Narcosis, traumatism of the tissues, disruption of the blood supply, and other unfavorable experiment conditions can easily distort the character of the electrical reaction of various regions of the brain to small concentrations of carbon dioxide.

K

Kappey, F., C. Albers, and R. Schmidt. The ventilatory CO_2 reaction of dog during heat tachypnea. Pfluger. Arch. Ges. Physiol. 275(3):312-326 (1962). Earlier work had shown that the CO_2 response curves (liters of minute ventilation per mm. Hg CO_2 partial pressure in arterial or venous blood) of the panting dog, while displaced in the direction of higher ventilation, are also flatter—of diminished slope—in comparison with control curves. This decrease in slope on increase in body temperature is the opposite of the findings in man. In the present work, the results earlier obtained in panting dogs in unsteady-state rebreathing experiments are confirmed in steady-state experiments involving the breathing of gas mixture containing CO_2.

Kellogg, R. H. Review of CO_2 acclimatization. Anesth. 21:634(1960).

Killion, P. L., and K. E. Schaefer. Tissue oxygen consumption and sleeping time during prolonged exposure to low concentrations of CO_2. Amer. J. Physiol. 183(1):44-45 (Oct. 1955). Oxygen consumption of liver tissue slices of guinea pigs and rats exposed up to 41 days to 1.5-percent CO_2 was not significantly changed compared with control values. However, there was a trend to decrease between the fifteenth

to forty-first day of exposure to CO_2. Values returned to initial levels during the 16-day recovery period on air following exposure to CO_2. The duration of the narcotic action of barbiturate was not significantly changed in guinea pigs after a 20-day exposure to 1.5-percent CO_2.

Kilmore, M. A., and H. F. Chase. Effects of hypercapnia and hypoxia during hypothermia. Anesth. Analg. (Cleveland) 41:435-441 (July-Aug. 1962).

King, B. G. High concentrations—short time exposure and toxicity. J. Indust. Hyg. and Toxicol. 31:365 (1949).

King, C. T. G., E. Williams, J. Mego, and K. Schaefer. Adrenal function during prolonged exposure to low concentrations of carbon dioxide. Amer. J. Physiol. 183(1):46-52 (Oct. 1955). The adrenal-pituitary interrelationship was investigated in normal and hypophysectomized rats and normal guinea pigs during exposure to 1.5-percent CO_2 for 11 to 15 or 28 to 42 days and during a 1.10-day period recovery in air. In normal and hypophysectomized rats, adrenal cortical activity was found to be increased during both

periods of exposure and recovery. The increase was indicated by a decrease of adrenal cholesterol and a significant eosinopenia and lymphopenia. Adrenal ascorbic acid content was reduced in normal rats during exposure to CO_2 but returned to the initial level during recovery. In guinea pigs, adrenal cortical activity was found to be increased only during the 28 to 42 day period of exposure to 1.5-percent CO_2 as shown by a significant eosinopenia and lymphopenia as well as a decrease of the adrenal cholesterol content. In both rats and guinea pigs, blood sugar remained at a normal level, apparently at the expense of liver and muscle glycogen stores. Glycogen returned to pre-exposure levels during the recovery period while muscle glycogen remained at a lower level.

King, C. T. G., E. C. Williams, J. L. Mego, and K. E. Schaefer. Effects of prolonged exposure to carbon dioxide in air on pituitary-adrenal interrelations in the male albino rat. Naval Medical Research Lab., AD 36750, New London, Conn. (16 Mar. 1954). Normal and hypophysectomized rats were exposed to 1.5-percent carbon dioxide for 42 days. Both groups of animals demonstrated a marked eosinopenia and lymphopenia, correlated with a drop in

adrenal cholesterol and ascorbic acid. The blood sugar was maintained at a normal level, apparently at the expense of liver and muscle glycogen stores. During this exposure to carbon dioxide, adrenal-cortical activity was increased and had not returned to initial levels when the animals were sacrificed at intervals during a ten-day recovery period on normal air. Results of the blood and adrenal studies indicate that prolonged exposure to 1.5-percent carbon dioxide produces a stress on the pituitary-adrenal system that is not reversed during a ten-day recovery period.

L

Lade, R. I., and E. B. Brown. Movement of potassium between muscle and blood in response to respiratory acidosis. Amer. J. Physiol. 204(5):761-764 (May 1963). Experiments were performed on anesthetized dogs in order to study the movement of potassium between the gastrocnemius muscle and blood during and following two hours of respiratory acidosis produced by breathing 30-percent CO_2 in O_2, and the difference between skeletal and cardiac muscles with respect to potassium movements during the first 10 minutes of breathing CO_2 and after return to air breathing. It was found that skeletal muscles lost potassium during hypercapnia. The loss was evident much earlier and was greater if the muscle was stimulated to intermittent contractions than if it was resting. The heart began to gain potassium a few minutes after CO_2 breathing began and lost potassium shortly after return to air breathing following 11 minutes of hypercapnia. There was no evidence for a contribution of skeletal muscles to the high transient elevation of the arterial potassium concentrations in the early posthypercapnic period.

Lambertsen, C. J., S. J. G. Semple, M. G. Smythe, and R. Gelfand. H^+ and pCO_2 as chemical factors in respiratory and cerebral circulation control. J. Appl. Physiol. 16:473-484 (1961).

Lambertsen, C. J. Carbon dioxide and respiration in acid-base homeostasis. Anesth. 21:642-651 (1960).

Lindhard, J. On the excitability of the respiratory center. J. Physiol. (London) 42:335-358 (1911).

Lloyd, B. B., M. G. M. Jukes, and D. J. C. Cunningham. The relation between alveolar oxygen pressure and the respiratory response to carbon dioxide in man. Quart. J. Exper. Physiol. 43:214(1958).

Loehning, R. W., H. Ueyania, and J. Ueda. Brain volume studies in animals: effects of hypercarbia, hypoxia, and intravenous urea. Brain enlargement occurred in craniotomized dogs after breathing 10 to 15-percent carbon dioxide mixtures for periods up to 4 hours. Brain volume returned to control levels when the animals again breathed room air. Following a similar period of hypercarbia, and when dogs breathed room air, cerebrospinal fluid pressure fell to levels below

those found initially. Craniotomized dogs breathing 6- to 10-percent oxygen mixture showed an acute increase in brain volume which returned to control level shortly after the animals breathed room air. Over a period of the next three hours, brain size in 6 of the 7 animals progressively enlarged and was still increasing at termination of the experiments.

Long, D. M. Jr., R. L. Clancy, and E. B. Brown. Role of abdominal viscera in the hyperkalemia produced by hypercapnia. Amer. J. Physiol. 204(5):753-756 (1963). The changes in plasma potassium concentration during and following breathing of high CO_2 mixtures were determined in dogs subjected to enterectomy, pancreatectomy hepatectomy, and abdominal evisceration. Plasma potassium increased during hypercapnia and increased still further in the immediate posthypercapnic period. The direction of these changes was the same as those in the control animals although some quantitative differences were observed. It was concluded that the hyperkalemia was not supplied by the liver, pancreas, or stomach and intestines since it appears in the absence of any or all of these organs.

Longson, D., and J. N. Mills. The failure of the kidney to respond to respiratory acidosis. J. Physiol. 122:81 (1953).

Longson, D., and J. N. Mills. Excess carbon dioxide and morning urine. J. Physiol. (London) 118:6 (1952).

Lubin, A. J., and J. C. Price. Effect of alkalosis and acidosis (producing changes in respiratory rate) on cortical electrical activity. J. Neurophysiol. 5:261-268 (1942).

Lundgren, N. P. V., et al. Respiratory response to oxygen and 4.1- and 6.2- percent CO_2 in air and oxygen at a ground level of 5000 feet. USAF School of Aviation Medicine, Project No. 21-1402-0001, Report No. 3, Randolph AFB, Texas (no date).

M

McGregor, M., R. E. Donevan, and M. M. Anderson. Influence of carbon dioxide and hyperventilation on cardiac output in man. Abstract in Fed. Proc. 21(2):135(1962). The effect of changes in ventilation and carbon dioxide tension or cardiac output was studied in seven normal human subjects in the supine posture using a dye dilution method. Voluntary hyperventilation of room air with resultant hypocapnia invariably produced an increase in cardiac output (mean, 38 ml. blood per liter increase in ventilation). Voluntary hyperventilation with maintenance of carbon dioxide tension at normal levels resulted in a smaller increase in cardiac output (mean, 15 ml. blood per liter). Hyperventilation produced by the inhalation of 8.4-percent carbon dioxide produced no change in cardiac output within the first 2 minutes but did produce an increase thereafter. The response of the cardiac output to hyperventilation is thus largely determined by the carbon dioxide content of the inspirate. The manner in which this takes place is uncertain. The higher cardiac output response at 2 minutes with hypocapnia may be the result of respiratory alkalosis. It might also be related to the increase in respiratory mechanical work per liter ventilation associated with the

fall in carbon dioxide. The reason for the late rise of cardiac output with hypercapnia is unknown.

Mills, J. N. Changes in alveolar carbon dioxide tension by night and during sleep. J. Physiol. 122:66 (1953).

N

Nakas, G. G., E. C. Jordan, and J. C. Ligou. Effects of a "CO_2 buffer" on the hypercapnia of apneic oxygenation. Amer. J. Physiol. 197(6):138-1316 (1959). Eight dogs maintained in apneic oxygenation for 60 minutes were given a 0.3M. intravenous infusion of 2-amino-2-V(hydroxymethyl-I, 3-propanediol (THAM) in a 0.3 percent NaCl solution at the rate of 1.1 Ml. per kg. per min. After 1 hour of apnea, arterial O_2 saturation was 100 percent, plasma CO_2 53.2mM. per L., plasma HCO_3^- 50.6mM. per l., arterial blood pH 7.37 and P_ACO_2 98 mm. Hg. Blood pressure remained close to the preapneic control period, and intracranial pressure did not change significantly. Plasma catecholamines levels did not change. There was a fall in hematocrit Na^+ and Cl^- plasma concentration while K^+ did not change. After a 20- minute lag, urine output equaled fluid input. Urinary pH was 7.54, HCO_3^- concentration 89mM. per l., THAM 85mM. per l. and 18 to 28 percent of the total CO_2 produced by the animal during apnea was recovered in the urine excreted during that time. All the animals survived, indicating that the dog will tolerate well a plasma concentration of CO_2 over twice its normal level when its two

fractions HCO_3^- and H_2CO_3 are in suitable proportion to maintain the biological neutrality of the internal environment (e.g., pH 7.40). In the presence of a normal pH and an elevated pCO_2 there is no measurable stimulation of the sympatho-adrenal system and the circulation is not altered.

Nash, C. W. Variation in the hypercapnic depression of the responses of vascular tissue to noradrenaline. Abstract in Fed. Proc. 21(2):107 (1962).

Navon, S., and A. Agrest. ATP content in the central nervous system of rats exposed to chronic hypercapnia. Amer. J. Physiol. 205:957-958 (Nov. 1963). Concentrations of adenosine triphosphate in the medulla oblongata and in the forebrain of rats exposed continuously to gas mixtures containing 6 to 8 percent CO_2 shows an exponential decay up to the twelfth day. The slope has a K = 0.10, and it levels off between the twelfth and fifteenth day of hypercapnia.

Nesell, O. The action of oxygen and carbon dioxide on the bronchioles and vessels of the isolated perfused lung. Acta Physiol. Scand. 21(73): (1950).

O

Okajima, M., and E. Simonson. Effect of breathing 6-percent carbon dioxide on ECG changes in young and older healthy men. Jour. Gerontol. 17(3):286-288 (July 1962). Electrocardiographic changes in 148 healthy men (88 older men and 60 younger men) produced by breathing a mixture of 6-percent CO_2 in air for 6 to 8 minutes were studied. The most prominent change in the electrocardiogram was a statistically significant decrease in the amplitudes of QRS and T frontal plane mean vectors which was more pronounced in the older men and may imply a decreased tolerance of older people to CO_2 excess.

Osorio, C., D.J. Jackson, J.M. Gartside, and A.W.G. Goolden. Effect of carbon dioxide and diphenylhydantoin on the partition of triiodothyronine labelled with iodine-131 between the red cells and the plasma proteins. Nature 196(4851):275-276 (1962). Diphenylhydantoin probably competes with both triiodothyronine and thyroxine for binding sites on TBP (Thyroxine binding protein). Carbon dioxide affects the binding power of α_2 and β-globins.

Otey, E.S., and T. Bernthal. Interaction of hypoxia and hypercapnia at the carotid bodies in chemoreflex stimulation of breathing. Fed. Proc. 19:373 (1960).

Otis, A. B., H. Rahn, and L. E. Chadwick. Effects of adding carbon dioxide to inspired oxygen on tolerance to high altitude; studies in respiratory physiology. Proc. Soc. Exper. Biol. Med. 70:487-490 (Mar. 1949).

P

Pierce, E. C. Jr., et al. Blood pCO_2 and brain oxygenation at reduced ambient pressure. J. Appl. Physiol. 17:899-908 (Nov. 1962).

Hyperventilation during breathing of 100-percent oxygen elevates the pO_2 of alveolar gas by the same amount that it lowers its pCO_2. Since the development of arterial hypocapnia causes cerebral vasoconstriction, brain oxygenation is drastically decreased even while arterial oxygenation is improved by hyperventilation. Administration of 30-percent CO_2 with oxygen at an ambient pressure equivalent to that at 39,000 feet prevented alkalemia and, in spite of hyperventilation, restored cerebral venous oxygenation to a level at least equivalent to that found when pure oxygen was breathed at rest at the same altitude. The respiratory minute volume during administration of CO_2 with O_2 was greater than when O_2 alone was breathed at reduced ambient pressure. Since neither arterial pO_2 nor cerebral venous pCO_2 values differed in these two experimental situations, the respiratory stimulation may represent the quantitative demonstration in man of a respiratory effect of CO_2 mediated by arterial chemoreceptor activation and unrelated to change in the level of central chemical stimulus.

Plass, G. N. Carbon dioxide and climate. Sci. Amer. 201(7):41-47 (July 1959).

Platts, M. M., and M. S. Greaves. The composition of the blood in respiratory acidosis. Clin. Sci. 16:695-708 (1957). The effects of acute and chronic respiratory acidosis on the composition of plasma and red cells of arterial blood have been investigated. Acute respiratory acidosis was induced in 4 normal persons by inhalation of 7 percent carbon dioxide in air. Thirteen severely emphysematous patients with chronic respiratory acidosis were studied. The carbon dioxide tension of the arterial blood was similar in these two groups of persons.

R

Ramlo, J.H., and E.B. Brown, Jr. Mechanism of splenic contraction produced by severe hypercapnia. Amer. J. Physiol. 197(5):1079-1082 (1959). Unilaterally adrenalectomized and bilaterally adrenalectomized mongrel dogs with both normal and denervated spleen were made hypercapnic by inhalation of 30-percent CO_2 in oxygen in order to determine the mechanism of the resulting splenic contraction. The results obtained indicate that splenic contraction in dogs breathing 30-percent CO_2 is mediated by both the splenic nerves and by the adrenal glands. The nerves appear to act more rapidly but contractions still occur in absence of all innervation. Neither bilateral adrenalectomy nor splenic degeneration alone completely blocked the splenic response in all animals, but of the two procedures the former appeared to be much more effective in this respect. In order to block completely the splenic response to inhalation of 30-percent CO_2, both denervation of the spleen and bilateral adrenalectomy were necessary.

Richards, J.B., and S.N. Stein. Effect of CO_2 exposure and respiratory acidosis on adrenal 17-hydroxycorticosteroid secretion in

anesthetized dogs. Amer. J. Physiol 188:1(1957). In dogs exposed to various concentrations (2.5 to 30 percent) of carbon dioxide for periods of 1 to 4 hours, adrenocortical stimulation was correlated with decreased pH and increased carbon dioxide content in the arterial blood. Maximal adrenocortical stimulation occurred in all dogs exposed to 20-percent carbon dioxide and this response persisted for as long as 4 hours. Hypophysectomy abolished the adrenocortical response to carbon dioxide exposure.

Rossen, R., E. Simonson and J. Baker. Electroencephalograms during hypercapnia Arch. Neurol. 8(4):373-381 (Apr. 1963). In 45 young and 64 older normal men, 12 of the young men (mean age 24.4 years) and 15 of the older men (mean age 60.7 years) showed slight changes on the EEG during breathing of a 6-percent CO_2 gas mixture. Older age seemed to correlate with a statistically highly significant greater increase in hyperventilation (with a slightly greater increase in alveolar CO_2 than in young men) in subjects with slight changes in EEG. Older age seemed to correlate also with a statistically significant greater increase in alveolar CO_2 in subjects with no essential changes in EEG.

S

Schaefer, K.E., G. Nichols and C. Carey. Acid-base balance and blood and urine electrolytes of man during acclimatization to CO_2. J. Appl. Physiol. 19(1):48-58 (Jan. 1964). Twenty subjects were exposed to 1.5-percent CO_2 for 42 days with control periods before and after the exposure. A slight uncompensated respiratory acidosis was present during the first 23 days, followed by a compensated respiratory acidosis. Deacclimatization was incomplete, even after 4 weeks of recovery in air. Arterial CO_2 tension increased 5 mm. Hg during exposure and remained at this elevated level during the first 9 days of recovery in air. In chronic respiratory acidosis, the concentration of chloride in the red cells and in plasma remained practically normal, indicating that the chloride shift does not operate. Cation exchange was observed under these conditions. Sodium increased while potassium showed an approximately equivalent decrease. Sodium and potassium balance studies indicated that only sodium exhibits a pattern paralleling the two phases of acid-base balance regulation, retention being followed by increased excretion. Body weight was maintained throughout the experiment in spite of a 24 to 30 percent reduction in food intake.

Schaefer, K.E., G. Nichols and C.R. Carey. Calcium phosphorus metabolism in man during acclimatization to carbon dioxide. J. Appl. Physiol. 18:1079-1084 (Nov. 1963). The calcium phosphorus metabolism was studied in 20 subjects who were exposed for 42 days at 1.5-percent carbon dioxide. Plasma calcium mirrored the changes of the pH, showing a decrease during the first 23 days of exposure, a return to initial levels during the latter part of the exposure, a marked rise above control values during the 8 to 9 day recovery period following exposure, and a return to normal values after 4 weeks of recovery. Changes in plasma calcium were found to correspond to changes in pulmonary CO_2 excretion indicating a significant role of bone CO_2 stores in acclimatization and deacclimatization to carbon dioxide. Plasma inorganic phosphorus was elevated throughout the exposure period and recovery period. At the end of the exposure period to CO_2, red cell calcium had increased and red cell phosphorus had decreased. After nine days, as well as after four weeks, of recovery on air, the calcium content of the red cell continued to increase and the inorganic phosphorus values remained lowered.

Schaefer, K.E. Acclimatization to low concentration of carbon dioxide. J. Appl. Physiol. 18:1071-1078 (Nov. 1963). In a large experiment, 21 subjects were confined in a submarine and exposed to 1.5-percent CO_2 over a period of 42 days, with a 9-day control period prior to and following exposure. The result showed no significant changes in performance or in basic physiological parameters such as blood pressure, pulse rate, weight, and body temperature. However, studies of respiration, acid base balance, and calcium phosphorus metabolism showed some remarkable adaptive changes.

Schaefer, K.E. A concept of triple tolerance limits based on chronic carbon dioxide toxicity studies. Aerospace Med. 32 (3):197-204 (Mar. 1961). Results of studies on chronic carbon dioxide toxicity are summarized and a time-concentration curve for adaptation to carbon dioxide is presented which is based on the time to reach a compensation respiratory acidosis. Experimental evidence demonstrating significant effects of elevated carbon dioxide tension in blood independent of pH changes is reported. Based on these findings, it appears doubtful whether long-term adaptation to even slightly increased pCO_2 is possible without altering normal physiologic processes and

producing histopathologic state. A concept of triple tolerance limits for carbon dioxide toxicity is proposed for three different levels of activity, including one at which no significant physiologic adaptive changes to carbon dioxide occur.

Schaefer, K.E., M. Hasson and H. Niemoeller. Effect of prolonged exposures to 15-percent CO_2 on calcium and phosphorus metabolism. Proc. Soc. Exp. Biol. Med. 107:355 (1961).

Schaefer, K.E. Experiences with submarine at atmospheres. J. Aviation Med. 30(5):350-359 (May 1959). The problems of submarine medicine experienced during prolonged submerged periods are reviewed. Thermal exchange in a normal apartment and a submarine are compared. The role of trace substances and ionization patterns of the atmosphere in confined spaces is discussed. Emphasis is placed on chronic carbon dioxide toxicity, which has been in the past the cardinal problem of submarine medicine. Differences in the combined effects of increased carbon dioxide and lowered oxygen under acute and chronic conditions are analyzed.

Schaefer, K.E. Respiratory pattern and respiratory response. J. Appl. Physiol. 13:1 (1958).

Schaefer, K.E., C.T.G. King, J.L. Mego, and E. Williams. Effect of narcotic level of CO_2 on cortical activity and carbohydrate metabolism. Amer. J. Physiol. 183(1):53-62 (Oct. 1955). Normal unanesthetized guinea pigs and normal, adrenalectomized, and hypophysectomized rats were exposed to 30-percent CO_2 in air and in O_2 for a period of 1 hour, followed by a 1-hour recovery period in air. Both CO_2 mixtures produced a severe acidosis in guinea pigs, superimposed in the case of 30-percent CO_2 in air by hypoxia. The blood CO_2 content remained high after recovery, while pH returned to a normal level. Exposure to 30-percent CO_2 in air but not in O_2 produced an increased adrenal cortical activity, indicated by a decrease in adrenal cholesterol and circulating lymphocytes and an increase in adrenal weight. Plasma potassium and sodium, blood glucose, and blood eosinophils increased in both groups while liver glycogen decreased and the total number of leukocytes remained unchanged. Muscle glycogen increased and lactic acid decreased under 30-percent CO_2 in air, with the opposite condition occurring under 30-percent CO_2 in O_2. Blood sugar in normal, adrenalectomized, and hypophysectomized rats increased significantly during exposure to both CO_2 mixtures. The

increase of blood sugar in the case of adrenalectomized rats, and the decrease of liver glycogen in guinea pigs during and after exposure to 30-percent CO_2 suggests an inhibition of the vago-insulin system under high CO_2 concentrations.

Schaefer, K.E. Group differences in carbon dioxide response of human subjects. Fed. Proc. 13(1[I]):128 (1954). Carbon dioxide response studied in 70 subjects using concentrations of 1.5-, 3.3-, 5.4-, and 7.5-percent CO_2 allowed differentiation of a low and a high ventilation group on the basis of a quantitative difference in ventilatory response to 5.4- and 7.5-percent CO_2. Subjects of these two groups also differed in their normal respiratory pattern in air. The low ventilation group showed a large tidal volume, small respiratory rate, and higher alveolar CO_2; the high ventilation group exhibited a small tidal volume, higher respiratory rate, and lower alveolar CO_2. Further group differences were as follows: the low ventilation group showed during exposure to 7-percent CO_2, a lower pulse rate increase, a lower blood sugar increase, and a lower eosinopenia.

Schaefer, K.E., et al. Respiration and circulation during and after inhalation of various concentrations of carbon dioxide. Marine Research Lab., Report No. 189 XI(9):(1952).

Schaefer, K.E., et al. Effects of inhalation of various carbon dioxide concentration on the inhibitory effect of light stimuli on alpha waves and muscle potential output of the forehead. Marine Research Lab., Report No. 192 XI (9): (1952).

Schaefer, K.E. Chronic CO_2 toxicity in submarine medicine. USN Medical Research Lab. Report No. 181, 10:156-176 (1951).

Schaefer, K.E. Respiration and acid base balance during prolonged exposure to 3 percent CO_2. Pflueger. Archiv. 251:689 (1949).

Schneider, E.C., and D. Truesdell. The effects on the circulation and respiration of an increase in the CO_2 content of the blood in man. Amer. J. Physiol. 63:155-175 (1922).

Schopp, R.T. Couplet periodic breathing response to high CO_2 and high and low O_2. Science (Washington) 132(3432):957-958 (7 Oct. 1960).
A breathing pattern is described which is characterized by a group of 2 breaths followed by a prolonged apnea and which may involve a mechanism different from at least one type of Cheyne-Stokes breathing. The pattern can be eliminated by breathing 9- or 10-percent CO_2. However, the pattern frequently persists during breathing of high O_2.

Sechzer, P.H., et al. Effect of CO_2 inhalation on arterial pressure, ECG and plasma catecholamines and 17-OHcorticosteroids in normal man. J. Appl. Physiol. 15(3):454-458 (May 1960). Twelve male volunteers inspired concentration of carbon dioxide in oxygen ranging from 7 to 14 percent for periods of 10 to 20 minutes. Respiratory minute volume arterial pressure, heart rate, and plasma concentration of epinephrine, norepinephrine, and 17-OHcorticosteroids increased in every subject during hypercarbia. Abnormal cardiac rhythm was infrequently observed. Following substitution of oxygen for the carbon dioxide-oxygen mixture, the altered measurements returned to normal over a period of roughly 10 minutes. Neither marked hypotension nor cardiac arrythmia was observed after correction of hypercarbia.

Shephard, R.I. The immediate metabolic effect of breathing carbon dioxide mixtures. J. Physiol. (London) 129(2):393-407 (29 Aug. 1955). The effects on oxygen consumption of breathing 5-percent carbon dioxide in air for up to 5 minutes were studied in three subjects. An observed increase above the estimated increase in oxygen consumption is attributed to an early elevation of cardiac output consistent with a

slight increase in pulse rate and a normal or slightly increased systemic blood pressure, an increase of 25 percent in cardiac work and, to a smaller extent, in the mechanical work of hyperventilation.

Shock, N. W., and M. H. Soleg. Effect of oxygen tension of inspired air on respiratory response of normal subjects to carbon dioxide. Amer. J. Physiol. 130:777-783 (1940).

Small, H. S., S. W. Weitznik, and G. G. Mahas. Cerebrospinal fluid pressures during hypercapnia and hypoxia in dogs. Amer. J. Physiol. 198(4):704-708 (1960). Cerebrospinal fluid pressure (CSFP) in the cisterna magna intraaortic and intrathoracic venous pressures were measured during apneic oxygenation (diffusion respiration) in dogs under light pentobarbital-succinylcholine anesthesia. CSFP doubled in 2 minutes and reached a peak of 375 percent above control in 10 minutes. During this time there were no consistent changes in arterial or venous pressures. Dogs ventilated with 5-, 10-, and 15-percent CO_2 showed a similar pattern. Cerebral vasodilatation caused by CO_2 is the probable mechanism in both groups. A sustained elevation of CSFP was observed throughout CO_2 administration for as long as 90 minutes. In all cases, there was a prompt return to control levels

on termination of the hypercapnia. Controlled ventilation with 8-percent O_2 caused an average 84-percent rise in CSFP, with a plateau occurring after 4 to 5 minutes. This was accompanied by marked increases in arterial and venous pressures. Cerebral vasodilatation probably occurs here also. During 90 seconds of asphyxia, the sharpest increase (176 percent) in CSFP occurred. This was accompanied by marked increases in arterial and venous pressures and represents the effects of hypoxia and hypercapnia combined.

Sokoloff, L. The effects of carbon dioxide on the cerebral circulation Anesthesiology 21(6[1]):664-673 (Nov. Dec. 1960). This paper reviews the effects of carbon dioxide on the cerebral circulation in various physiological and pathological states (during hypoxemic acidosis and alkalosis, anesthesia, increased blood pO_2, and cerebrovascular diseases). In general, CO_2 causes cerebral vasodilatation and peripheral vasoconstriction, and has been found to hasten recovery from general anesthesia to protect against the deleterious effects of hypoxia on the central nervous system, and to increase the tolerance to positive radical acceleration.

Stone, W.E., J.E. Webster, J. Kopala, and E.S. Gurdjian. Effects of carbon dioxide administered on cerebral metabolism in hypoxia. Fed. Proc. 5:101-102 (1946).

T

Tabusse, L., and P. Biget. The CO_2 test. Med. Aero. (Paris). 7(2):197-206 (1952). The carbon dioxide test, devised by Santenoise, represents a practical application of the facts that increasing amounts of CO_2 induce hyperventilation which manifests itself in a proportional increase of thoracic breathing movements. When the thoracic movements of healthy subjects, breathing air mixtures containing up to 2-percent CO_2, are recorded graphically on a revolving drum, the resulting pneumograph consists of a band of equally wide pulsations. When the CO_2 content is increased, pulmonic ventilation and thoracic movement are augmented, causing an increase in the amplitude of the pneumograph pulsations (a characteristic cone-shaped expansion of the pneumograph). The method is of diagnostic significance, as it was observed that in persons suffering from certain respiratory defects (such as asthma and silicosis) the hyperventilatory response to CO_2 sets in at concentrations considerably higher than 2 percent (up to 12 percent). The test has also found application in aviation medicine, where hypoexcitability to CO_2 (up to concentrations of 10 percent) has been correlated with abnormal lack of physical resistance to altitudes

(altitude hypoçapnia). Inclusion of the test in routine selective physical examinations of pilots, as well as in later physical check-ups, is recommended.

Thorner, M. W. The effect of carbon dioxide on the electroencephalogram at ground level. AAAF Project No. 215. Report No. 1 (no date).

Turner, J., et al. Effects of 0.08 and 0.8 atmospheres of inspired pO_2 upon cerebral hemodynamics at a constant alveolar pCO_2 of 43 mm. Hg. Fed. Proc. 16(1[1]):130 (Mar. 1957). Inhalation of 8-, 21-, and 80-percent oxygen at 1 atmosphere was carried out at an alveolar carbon dioxide tension (pCO_2) adjusted in 6 normal subjects to a mean of 43 mm. Hg in each of the experimental conditions. In the absence of significant alterations of alveolar or arterial pCO_2, 80-percent O_2 produced no change in brain circulation or cerebral vascular resistance from control levels obtained during 21-percent O_2 breathing. This suggests that the cerebral vasoconstriction normally associated with O_2 inhalation is predominantly an indirect effect, secondary to arterial hypocapnia. Inhalation of 8-percent O_2, resulting in arterial and cerebral venous pO_2 of 39 and 28 mm. Hg respectively decreased cerebral vascular resistance 29 percent,

increased brain blood flow 36 percent, and left cerebral oxygen consumption unaltered. The observed degree of cerebral vasodilatation represents the action of low pO_2, unmodified by antagonistic effects of the hypocapnia normally associated with hypoxia.

Van Goor, H. Carbonic anhydrase, its properties, distribution, and significance for carbon dioxide transport. Enzymologia 3:75-164 (1948).

Van Ypersele De Strihou, C., P. F. Gulyassy, and W. B. Schwartz. Effects of chronic hypercapnia on electrolyte and acid-base equilibrium: III. Characteristics of the adaptive and recovery process as evaluated by provision of alkali. J. Clin. Invest. 41:2246-2253 (Dec. 1962).

W

Weatherly, J. H., and A. Burt. Individual variation in respiratory response to carbon dioxide at altitude. U.S. Naval School of Aviation Med. Project No. X-402 (AV-216-F), Research Report No. 1, Pensacola, Fla. (25 July 1944).

White, C. S., J. H. Humm, E. D. Armstrong, and N. P. V. Lundgren. Human tolerance to acute exposure to carbon dioxide: I. Six-percent carbon dioxide in air and in oxygen. J. Aviation Med. 23(5):439-455 (1952). Test subjects (physicians and pilots) were exposed to the breathing of about 6-percent CO_2 in air or in oxygen (at an altitude of 5,000 feet above sea level). All but one subject completed 16 minutes of inhaling CO_2 without serious symptoms. The breathing had no significant influence on the outcome of a card-sorting test; the expiratory minute volume was significantly increased in the two experimental groups (from 11-12 to 30-38 liters per minute), the alveolar CO_2 tension rose in the course of the experiment. A CO_2 breathing test should be given to all pilot candidates as an indoctrination procedure.

White, C. S. Estimated tolerance of human subjects to various CO_2 time concentrations: calculations of CO_2 percentage equivalents at sea level and various pressure altitudes. Lovelace Foundation Project No. 200, Appendix No. 1, Report No. 2, Aviation Medical Consultants Report to the Douglas Aircraft Co. Lovelace Foundation, Albuquerque, N. Mex. (11 Oct. 1948).

White, C. S. Estimated tolerance of human subjects to various CO_2-time concentrations. Lovelace Foundation Project No. 200, Report No. 2, Medical Consultants report to the Douglas Aircraft Co., Lovelace Foundation, Albuquerque, N. Mex. (27 July 1948).

Whitehorn, W., and J. W. Bean. Cardiac changes induced by O_2 at high pressure CO_2 and low O_2 as manifest by the electrocardiogram. Amer. J. Physiol. 168(2):528-537 (1952). Electrocardiograms were taken of decerebrated dogs exposed to oxygen pressures of 60 pounds. Comparisons were made with the effects of high CO_2 (11.5 percent) and low O_2 (8 percent) on another group of animals. A great similarity between the effects of hypercapnia and hypoxia on the one hand and high-pressure oxygen on the other was observed. Pronounced

bradycardia and an increase in P-R interval were found to be common symptoms. Denervation of the heart, while delaying the onset of bradycardia and slowing A-V conduction, did not prevent the occurrence of these phenomena.

Winder, C. W., Combination of hypoxic and hypercapnic stimulation of the carotid body. Amer. J. Physiol. 136:200-206 (1942). The isolated carotid body regions of anesthetized dogs were perfused by means of a continuous artificial circuit with continuous gaseous equilibration of the basal perfusion fluid (heparinized blood and Locke's solution). Brief substitution of experimental fluids equilibrated with gases high in CO_2, low in O_2, or a combination of the two, yielded reflex respiratory responses so that the combination effect on minute volume of CO_2 and low O_2 was approximately equal to the sum of their individual separate effects. The results are interpreted in terms of the theory that intracellular pH is a factor in the control of chemoreceptor activity. The chemoreceptors are considered as one of several probable sites for mutual facilitation of hypoxic and hypercapnic stimulation of respiration.

Wiskont-Buczkowska, H. Gas exchange in hypoxic-hypercapnic hypothermia in rats. Acta. Physiol. Pol. 8(3-3a):567-568 (1957).

Woodbury, D. M., and R. Karlic. The role of carbon dioxide in the nervous system. Anesth. 21(6[1]):686-703 (Nov.-Dec. 1960). It has been shown that various concentrations of CO_2 exert inhibitory and excitatory effects on the central nervous system (CNS). In addition, several drugs that mimic the effects of CO_2 on the CNS possess this activity by virtue of their ability to alter the tissue level of CO_2. The mechanism of the CNS action of CO_2 appears dependent upon specific electrolyte and amino acid changes. Carbonic anhydrase is important in the regulation of the level of brain CO_2 and excitability and the role of carbonic anhydrase in the brain is ultimately concerned with the conversion of metabolically produced H_2CO_3 to CO_2. Furthermore, this functional role of the enzyme appears associated with the soluble fraction of the cell.

Woodbury, D. M., et al. Effects of oxygen and carbon dioxide inhalation on brain excitability in mice and rats. Fed. Proc. 14(1[I]):395-396 (Mar. 1955). The electroshock seizure threshold (EST) of the brains

of mice and rats was decreased by hypoxia and by decreases in the concentration of O_2 in inhaled air and increased by hyperoxic increases. The decreased threshold resulting from 10-percent oxygen could be counteracted by simultaneous administration of 12.5-percent carbon dioxide. Increases in carbon dioxide progressive increased the EST, while a concentration of 30 percent had no effect. Rapid withdrawal of mice from high concentrations of carbon dioxide resulted in clonic or tonic-clonic seizures within 2 minutes.

Z

Zheludkova, T. N., V. P. Zagryadskiy, O. Yu. Sidorov, and Z. K. Sulimo-Samuylio. Oxygen in reducing the unfavorable elevated carbon dioxide concentration of the organism. AFSC N65-17807 Foreign Technology Div., Wright-Patterson AFB, Ohio. Rabbits kept in an airtight chamber, in which the O_2 and CO_2 concentrations could be regulated, show a favorable effect of high-O_2 concentration on the state of hypercapnia. A prolonged exposure to an atmosphere containing 3- to 5-percent CO_2 and 35-percent O_2 resulted in less pronounced physiological effects, faster recovery, and greater tolerance to transverse radial acceleration stress than under conditions of 3- to 5-percent CO_2 and 21-percent O_2.

AUTHORS UNKNOWN

Report on oxygen-carbon dioxide mixtures. J. A. M. A. 114:1077-1079 (1940).

The narcotic properties of CO_2. New York State J. Med. 44:597-602 (1944).

V. HYPERTHERMIA

A

Adolph, E. F. Physiology of man in the desert, p. 49. New York: Interscience Publishers (no date).

Agersborg, H. P., G. Barlow, and R. R. Overman. Ionic and Hemodynamic alterations in hyperthermic dogs. Abstract in Fed. Proc. 15 (1[1]): 1-2 (March 1956). A mixture of T-1824 and Na^{24}, K^{42} or P^{32} was administered intravenously to dogs subjected to an ambient temperature elevating the rectal temperature to 42.5°C. which was maintained for one hour. Sodium disappearance rate, heart rate, respiratory rate, hematocrit, plasma protein concentrations, and plasma and cell potassium concentrations were significantly increased; cardiac output, plasma volume, and blood pressure were decreased. No change was seen in isotope "spaces", blood volumes, and potassium and phosphorus rates of disappearance. Electrocardiograms exhibited a strong similarity to characteristics of hyperpotassemia.

B

Barlow, G., H. P. Agersborg, and H. E. Keys. Blood levels of 17-hydroxy-corticosteroids in the hyperthermic dog. Proc. Soc. Exper. Biol. Med. 93(2):280-284 (Nov. 1956). Dogs exposed to heat (body temperature of 42.5°C. for one hour) showed increases in plasma 17-hydroxy corticoid and potassium levels, and no change in plasma sodium. Red blood cell Na and K levels were increased. Total circulating plasma K was unchanged, but total circulating Na was decreased, presumably by transfer into muscle and red blood cells. Possible mechanisms for the pronounced increases in 17-hyproxycarticosteroid concentrations include thermal stimulation of adrenal cortical function, either directly or through ACTH impairment of the rate of hormone destruction in the liver, and a decreased rate of utilization or destruction in peripheral tissues of the body. Increase in plasma K is attributed to plasma concentration or to increased respiratory muscle activity.

Bartlett, D. J., and D. G. C. Gronow. The effects of heat stress on mental performance. AD 30 748 (Aug. 1953). Investigations were made into the possible effects of different kinds of heat stress upon anticipatory perception and judgement. Several displays represented aircraft

moving from square to square on a card; in some instances, these movements would result in aircraft collision. Subjects were required to decide how many, if any, collisions would occur on any given card, which aircraft would be affected, and where collisions would occur. The climatic conditions experienced were at room temperature (60°/70°F), 80°/70°F dry/wet bulb, 90°/80°F dry/wet bulb, and 100°/90°F dry/wet bulb. The 24 subjects were exposed to the hot conditions for 1/2 hour before testing and during the test periods (1/2 hour). While performance was significantly affected by increase in number of aircraft presented and by card display size, no important effect was caused by heat level or the assigned speed or movement of the aircraft.

Bass, D. E., and A. R. Lind. The economic period of daily exposure to heat for the development of acclimatization. Presented at the Physiological Society, Guy's Hospital Medical School Meeting, 13 Jan. 1961. Four groups of volunteer subjects were submitted to 9 successive days of exposure to a climate with dry-and wet-bulb temperatures of 48.9 to 27.6°C, and an air movement of about 200 feet (61 meters) per minute. All men walked at 3.5 miles

(4.8 kilometers) per hour on a level treadmill. Each group was subjected to a different daily routine involving one 50-minute exposure or two 100-minute exposures. The induction and assessment of acclimatization may be more satisfactorily accomplished when men are required to work in the heat for a continuous period which is sufficiently long to permit the establishment of thermal equilibrium. This result was only achieved in exposures longer than 50 minutes in the present experiment. A daily exposure of 100 minutes was the most economic way to develop full acclimatization.

Bass, D. E., et al. Mechanisms of acclimatizations to heat in man. Medicine (34:323-380 (no date).

Bean, W. B., and L. W. Eichna. Performance in relation to environment temperature; reactions of normal young men to simulated desert environment. Fed. Proc. 2:144-164 (no date).

Belding, H. S., and F. L. Hatch. Relation of skin temperatures to acclimation and tolerance to heat. Fed. Proc. 22:881-883 (May-June 1963).

Bell, C. R., and K. A. Provins. Effects of high temperature environmental conditions on human performance. J. Occupat. Med. 4:202 (1962).

Benzinger, T. H. On physical heat regulation and the sense of temperature in man. Proc. Nat. Acad. Sci., (Wash.) 4.5:645-659 (no date).

Blockley, W. V. Heat storage rate as a determinant of tolerance time and duration of unimpaired performance above 150°F. Fed. Proc. 22:887 (May-June 1963). The slope of the straight line relating mean body temperatures and exposure time in non-compensable heat-stress situations yields an index of body heat storage rate which is a reliable predictor of tolerance time. The storage rate shows good agreement with that resulting from solution of the heat balance equations; thus, a biothermal analysis to establish the magnitude of all heat gain and loss terms for the body permits the estimation of the tolerance duration of exposure to any severe heating condition. The duration of unimpaired performance capability for a complex psychomotor task was approximately 75 percent of the

tolerance time. The beginning of performance deterioration coincided with the onset of distress symptoms which are associated with the tolerance end-point. Large individual differences in the extent of terminal deterioration were related to the skill level in the task, as indicated by control sessions at comfort temperatures.

Blondheim, S. H. Relationship between ambient temperature and acetylating capacity of human blood. J. Appl. Physiol. 18:955-958 (Sept. 1963). The ability of human blood to acetylate P-aminobenzoic acid, determined in vitro, varied directly with the ambient temperature to which the subject was exposed before blood was drawn. This ability was demonstrated by 135 determinations of the acetylating ability of the blood of 49 subjects over a 3-year period, and also in acute experiments in which subjects were exposed to 6 and 37°C for up to 2 hours. Variations in the acetylating ability of blood may reflect the activity of metabolic mechanisms involved in thermal homeostasis.

Braner, R. W., et al. Reversible and irreversible changes in liver at temperatures approaching critical upper level. Fed. Proc. 22:724-728 (May-June 1963).

Brehner, D. F., D McKerslake, and D. G. Soper. Some effects of exposure to an environment of saturated air at mouth temperature. J. Physiol. (London) 162:(June 1961). Subjects were weighed continuously while exposed to an environment of saturated air at mouth temperature. After the first 10 minutes, mouth temperature increased steadily with time. The rate of weight loss at first increased with time and rising temperature, later reached a maximum, and then decreased. The most constant parameter was the maximum increase in rate of weight loss for a temperature rise of 0.4°C. (g). The value of g for an exposure in the afternoon could be predicted (with confidence limits of 95-percent) from the observed value the same morning within about ±30 percent. The value of g and the rate of weight loss at 38.4°C. (near the maximum) increased several times during daily exposures and terminated at mouth temperature of 38.4 to 38.6°C. The use of this type of exposure as an index of the sensitivity of the sweating mechanism is discussed.

Breuninger, H., and W. Schmidt. The reaction of the blood pressure to artificial hypothermia and hyperthermia and its pharmacological inhibition. Naunyn-Schmiedeberg Arch. Exp. Path. 2253(3)251-259

(1955). Shifts of blood pressure upon rapid cooling and rewarming of the organism were studied in the rat, guinea pig, and golden hamster. The rise of blood pressure during cooling and overheating is a centrally regulated emergency function. This response was inhibited through a central block (completely by anesthetics; partially by antihistaminics), or a peripheral block (primarily by adrenolytics including megaphen). Morphine and parasympatholytics were without effect. Definite relationship did not exist between the inhibitory effects of these drugs and their analgesic or antipyretic value. The locus for inhibition of the emergency function varies for different drugs with a central action.

Brewin, E. G., R. P. Gould, F. S. Nashat, and E. Neil. The influence of temperature on the relationship between blood CO_2 tension and plasma pH. J. Physiol. 127:19-20 (1955).

Broceha, L., M. E. Maxwell, P. E. Smith, Jr., and G. J. Stopps. Discrepancy between heart rate and oxygen consumption during work in warm environment. J. Appl. Physiol. 18:1095-1098 (Nov., 1963). These experiments compare the usefulness of oxygen consumption

and heart rate as indicators of the strain produced by repetitive work in various environments. When the length of the rest periods was determined by the time required for oxygen consumption to return to its resting level, a steady state of heart rate and oxygen consumption was achieved in a comfortable environment. In warm surroundings, oxygen consumption reached a steady state but the heart rate increased during repetitive work cycles. When the duration of the rest periods had been arbitrarily fixed, both oxygen consumption and heart rate reached constant steady states in repeated work cycles with light environmental stress. With severe stress, oxygen consumption remained at the same average value from cycle to cycle and failed to indicate the presence of accumulated strain which was revealed by increasing heart rates.

Brown, E. B. Tolerance of the hyperthermic dog to carbon dioxide. School of Aviation Med., AD 113 245, Randolph AFB, Texas. Tolerance of the hyperthermic dog to elevated CO_2 tensions in the inspired air was determined. Results were compared with those of similar experiments obtained on normothermic dogs. A body temperature elevation of 2 to 3°C. produced by inhalation of warm

moist oxygen and by warming with infrared lamps decreased the tolerance of dogs to elevated CO_2.

Brümer, H., and K. E. Klein. Effects of high temperature and acclimatization on the efficiency of pilots. Deutsche Versuchsanstalt fur Luftfahrt (Mulheim), 125:21-31 (June 1960). A method is proposed for the evaluation of environmental heat stress by reference to physical index of effective temperature (heat, humidity, and air speed) in combination with a physiolog stress index of pulse rate and body temperature. A rectal temperature of 38.3°C. and a pulse rate of 115 per minute are the characteristic values for the physiologic tolerance limit to heat. Studies of the predictive value of the indices under various environmental conditions have shown that heat tolerance is dependent on the interrelation of rectal temperatures and pulse rate, and that acclimatization to heat increased tolerances by 5 to 6°C. air temperature.

Buskirk, E. R., Welch, B. E. and Iampietro, P. F. Variations in resting metabolism with changes in food, exercise and climate. Army Medical Nutrition Lab. (Denver), Report No. 215:1-19 (14 Oct. 1957).

C

Carlson, L. D., and K. J. K. Buettner. Thermal stress and physiological strain. Fed. Proc. 16:609 (1957)

Carnazzo, A. On the reactions to ambient hyperthermia: III. Effect of ambient hyperthermia on the potassium level curve. Boll. Soc. Ital. Biol. Sper. (Napoli) 29 (8):1552-1554 (July-Aug. 1953). Subjects exposed to heat (43 to 45°C.) showed a variable increase in blood potassium level in relationship to the same subjects at temperatures of 25 to 30°C. Experimental hyperthermia acting as a body stress has a marked effect on adrenocortical activity. Under this condition, blood potassium curve determinations may be indicative of adrenocortical functions.

Cassuto, Y. The thermogenic role of the liver in the heat-acclimated hamster (Mesocricetus Auratus). Canad. J. Biochem. Physiol. 41:1840-1842 (Aug. 1963).

Collins, K. J. Endocrine control of salt and water in hot conditions. Fed. Proc. 22:716-720 (May-June 1963).

Consolazio, C. F., et al. Nitrogen excretion in sweat and its relation to nitrogen balance requirements. J. Nutrit. 79(4):399-406 (Apr. 1963). The results of two experiments show that a considerable quantity of nitrogen is lost in sweat under conditions that produce sweating. Values averaged 149, 189, 241 mg. per hour during exposure to environmental temperatures of 70, 85, and 100°F, for men performing moderate daily physical activities. Men performing a daily minimum of physical activity at 100°F. showed a decrease excretion of 200 to approximately 300 mg. per hour, after acclimatization. The nitrogen losses in sweat increased with an increase in physical activity and sweat rate. The increased losses in sweat, even after acclimatization, are not compensated by decreased nitrogen losses from the kidneys and alimentary tract. As a result, the protein requirements of 0.35 g/kg. body weight should be increased by at least 13 to 14 percent to compensate for the nitrogen losses in sweat. The free amino acids excreted in sweat average more than 1 g. during a 7-1/2 hour exposure to 100°F. Data are also presented for other nitrogen compounds in sweat including urea nitrogen, ammonia, creatinine, and uric acid.

Consolazio, C. F. The sweat excretion of nitrogen in relation to balance, environment, and physical activity. U. S. Army Med. Res. Nutr. Lab., Report No. 270:22(1 Oct. 1962).

Cooper, T., V. L. Willman, and C. R. Hanlon. Effects of hyperthermia on blood volume and total peripheral resistance. Abstract In Fed. Proc. 20 (1[I]) 212 (1961).

Criscuolo, P. Blood volume in rats chronically exposed to altitude in combination with heat. AF School of Aviation Med. Report 58-36 (Jan. 1958).

Criscuolo, D., H. B. Hale, and R. B. Mefferd. Oxygen transportation, utilization, and storage in rats acclimated to altitude at differ : temperatures. J. App. Physiol. 13(3):353-356 Nov. 1958. Oxygen transportation, utilization, storage, and related functions were studied in rats exposed to simulated altitude (18,000 feet) at three different temperatures (5, 24, and 36°C) for periods in excess of 3 months. Liver, heart, kidney, and adrenal weight were altered only where thermal influences were involved. Adrenal weight in altitude cold was greater than in cold alone. The oxygen transportation

function was normal in cold at altitude, but was depressed in altitude heat. Liver succinic dehydrogenase activity was elevated in all altitude groups, but more so in heat and cold. Adrenal heat was elevated most in altitude cold. Oxygen storage was unaffected by thermal factors.

Cullumbine, H., and S. Miles. The effect of atropine sulfate on men exposed to warm environments. Quart. Jour. Exper. Physiol. (London) 41 (2):162-179 (Apr. 1956).

Cunningham, D. J.C., and J. L. H. O'Riordan. Effects of raising the body temperature in man. Abstract in J. Physiol. (London) 131(3):14-15 (28 Mar. 1956). The respiratory effects of increased body temperature produced by high environmental wet-bulb temperatures were investigated in five subjects. The decline in alveolar CO_2 pressure and the increase in ventilation observed at elevated temperatures were often greater when the temperature was rising than when it was at a steady elevated value. Below the normal alveolar CO_2 level, sensitivity to increased ventilatory CO_2 was reduced by increased temperature, while at and above the normal level, sensitivity was doubled.

Cunningham, D. J. C., and J. L. H. O'Riordan. The effect of a rise in the temperature of the body on the respiratory response to carbon dioxide at rest. Quart. J. Exper. Physiol. (42):329-345 (no date).

D

Dasler, A. R. Physiological responses of human subjects to heat in a sheltered environment. Forty-seventh annual Meeting of the Federation of American Societies on Experimental Biology (no date). Seasonal differences in 2-week residence periods in a 100-man underground protective shelter were studied using healthy young men as subjects. In the 2-week winter trial (96 subjects), temperature conditions did not exceed 82°F and 65-percent RH—78°F effective temperature (ET). In the summer trial (92 subjects), the maximum temperature was 91.5°F, with 90-percent RH (89°F ET). Based on 2-hour summer readings, the average ET was 85°F the first week, with an over-all average ET at 82°F. for the 2-week trial. Indices of heat strain included body temperature (oral and skin), resting pulse, and sweat rate (evaporative and total extra-renal water loss). Water and electrolyte balance (daily water intake, body water by deuterium dilution, 24-hour urinary output, and excretion of electrolytes), urinary 17-hydroxycorticosteroids, and physical fitness using a modified Harvard Step Test were also measured. Significant differences in the results of the two trials were observed in heat strain indices, water intake (which correlated

well with ET (R=0.91), and clinical disorders related to heat. No significant changes in physical fitness were observed as a result of the 2-week confinement periods.

Delahaye, R. P., and J. Gavanou. How does the body adapt to the Saharan climate? Presse Therm. Climat. 99:186-188 (Nov-Dec. 1962).

Depocas, F. Glucose metabolism in warm-and cold-acclimatized rats. Fed. Proc. 19 (5):106-109 (Dec. 1960).

E

Edholm, O. G., R. H. Fox, R. K. Macpherson. The effect of body heating on the circulation in skin and muscle. J. Physiol. (London) (134):612-619. Blood flow in the human forearm during heating by partial immersion was measured by water plethysmography before and after iontophoresis of adrenaline to occlude skin circulation. Occlusion of skin circulation eliminated entirely the increase in blood flow normally associated with body heating. The increase in blood flow during heating is due wholly to changes in the circulation of the skin and superficial tissues.

Eichna, L. W., W. F. Ashe, W. B. Bean, and W. B. Shelley. The upper limits of environmental heat and humidity tolerated by acclimatized men working in hot environments. J. Industr. Hyg. 27:59 (1945).

Eichna, L. W., et al. Thermal regulation during acclimatization in a hot, dry (desert type) environment. Amer. J. Physiol. (163):585-597 (no date).

Elias, H. Structural adaptation of the kidney to arid and humid environments. AD 410575 (no date).

F

Ferres, H. M. et al. The contribution of radiant heat to environmental stress. Med. Res. Counc. Spec. Rep. (London) 298:95-157 (1960).

Fox, R. H., R. Holdsmith, I. F. G. Hampton, and R. T. Wilkinson. The effects of a raised body temperature on the performance of mental tasks. J. Physiol. (London) 167(1):22-23 (June 1963). Mental performance was compared in subjects at normal and at three other levels of body temperature (37.3, 37.9 and 38.5°C.). The effects of each temperature level were tested once during each of the four 4-day periods. When body temperature was elevated to 38.5°C, both speed and accuracy in mathematics was impaired ($P < 0.02$) whereas vigilance was improved ($P < 0.05$). In accuracy of mathematics and in vigilance, a similar trend was seen at the two lower body temperatures. Subjects became heat-acclimatized but the effects of an elevated body temperature on mental performance did not diminish as acclimatization developed. Raising body temperature directly affects mental performance and the change observed may be

either an improvement or impairment of performance depending on the type and conditions of the test.

Fox, R. H., R. Goldsmith, D. J. Kidd, and H. E. Lewis. Acclimatization to heat in man by controlled elevation of body temperature. J. Physiol. (London) (166):530-547 (1963). A method of achieving a controlled elevation of body temperature in a number of subjects simultaneously is described as well as the acclimatization response evoked by the procedure. Exposure to heat caused a decrease in the heart rate while working, lowered skin and deep body temperatures, increased the sweat rate, and subjectively, lessened sense of discomfort. This traditional approach had a number of limitations and made it difficult to determine whether effects such as lowered heart rate are an adaptation to raised body temperature, or simply result from lowered body temperature which is secondary to improved heat-eliminating capacity.

Fox, R. H., R. Goldsmith, and D. J. Kidd. Changes in peripheral blood flow with heat acclimitization. J. Physiol. (London) 127 (2):57-58 (July 1961). Nine male subjects acclimatized to daily body temperature elevation levels (37.3 to 38.5°C) for 3 different

durations (1/2 to 2 hours) were tested both before and after acclimatization for peripheral blood flow response to body heating. The subjects were heated to an oral temperature of 38.5°C. and body temperature, blood flow in the hand and forearm, and skin changes in the chest and in one ear pinna were measured. Blood flow at the end of the heating period was higher in the forearm, hand, chest, and ear after acclimatization.

Fox, R. H. Acclimatization of the sweating mechanism in man. J. Physiol. (London) 127(2):56-57 (July 1961). Healthy subjects were exposed to hot environments in which their oral temperature reached 37.3°, 37.9°, or 38.5°C for 1/2 to 2 hours daily for 12 days. The effects of acclimatization on perspiration rate (when performing a controlled physical activity in a standard "hot climate") were studied. The subjects maintained at the lowest body temperature level did not show an increase in sweat rate. Subjects maintained at the highest body temperature level exhibited a progressive increase which was most marked for the subjects with the longest exposure (120 percent) and least for those of the shortest exposure (50 percent). Small elevations in body temperature maintained for

short periods daily, are capable of causing an acclimatization of the sweating mechanism in man.

Fox, R. H., R. Goldsmith, D. J. Kidd, and H. E. Lewis. The mechanism of the increase in sweating capacity induced by heat acclimatization. J. Physiol. (London) 157:57-58 (no date).

Fox, R. H., and S. M. Hilton. Bradykinin formation in human skin as a factor in heat vasodilation. J. Physiol. (London) (142):219-232 (no date).

Frada, G., and L. Salamone. On the reaction to ambient hyperthermia. II. Modifications in some blood chemical components. Boll. Soc. Ital. Biol. Sper. (Napoli) 29(8):1549-1552 (July-Aug. 1953). Fifteen subjects at rest following exposure to high environmental temperature (43 to 45°C) for two hours revealed a moderate reduction in blood calcium, potassium, and sodium and a moderate increase in chlorine and sugar contents. A reduction in blood volume was noted but no significant change occurred in blood urea nitrogen.

Frada, G., and L. Salamone. On the reactions to ambient hyperthermia: I. Hematological investigations. Boll. Soc. Ital. Biol. Sper. (Napoli) 29(8):1546-1549 (July-Aug. 1953). Hemotological studies on 15 normal persons exposed to heat (43 to 45°C) revealed variable erythrocytosis, leukocytosis, neutrophilia and mononucleosis. In addition, an increase in blood coagulation time and hemoglobin content were noted along with a decrease in the total blood volume. Four subjects exhibited moderate leukopenia.

Frankel, H. M., J. P. Ellis, Jr., and S. M. Cain. Tissue oxygenation during progressive hyperthermia. Presented at the forty-seventh annual meeting of the Federation of American Experimental Biology, 1963: Abstract in Fed. Proc. 22(21):175 (1963). During hyperthermia, arterial hypoxemia does not occur until after obvious failure of respiration. The occurrence of stagnant tissue hypoxia (as evidenced by anaerobic glycolysis) may contribute to the failure of cardio-pulmonary systems.

Furman, K. I., and G. Beer. Dynamic changes in sweat electrolyte composition induced by heat stress as an indication of acclimatization and aldosterone activity. Clin. Sci. 24:7-12 (Feb. 1963).

Gellhorn, E. Discussion on temperature and the automic nervous system. Acta. Neuroveg. (Vienna) 11)1-4):90-93 (1955). Cooling of the body of cats (25 to 20°C.) by immersion decreases the sympathetic excitability of the hypothalamus, as shown by the reduction of the rise in blood pressure and pulse rate, and a decrease in the contraction of the nictitating membrane. The enhancement of the depressor effect of acetocholine, mecholyl, and histamine on blood pressure. Raising of the body temperature from 37 to 40°C increases the sympathetic excitability of the hypothalamus, whereby hypothalamic stimulation evokes stronger sympathetic reactions than at normal body temperatures.

Gerbraudy, J., E.S. Snell, and Crauston, W.I. Oral, rectal, and esophageal temperatures in relation to central temperature control in man. Clin. Sci. 13:615-624 (no date).

Gerking, S.D., and S. Robinson. Decline in the rates of sweating of men working in severe heat. Amer. J. Physiol. (147):370-378 (no date).

Gettler, D. T., F. M. Colip, and P. R. Schloert. The effect of kidney hyperthermia on renal tolerance to total ischemia. Surg. Gynecol. and Obstet. 112(5):559-563 (1961). There is a reduction in the permissible period of renal ischemia with either local warming of the kidney up to 41°C. or systemic hyperthermia produced with endotoxin. After contralateral nephrectomy, the critical limiting temperature time range of renal ischemia in dogs appears to be relatively constant at 35 to 40 hours between 5 and 41°C, but can be increased by allowing a 3-week recovery period before the contralateral nephrectomy.

Gex, R. C. Space travel and human thermal limits: a selected bibliography. N63-21305. This selected bibliography, partially annotated, is divided as follows: physiological mechanisms of temperature regulation, metabolism, thermal properties of tissues, compact criteria, thermal indices and units, compensable zone (high temperature), compensable zone (low temperature), hyperthermic zone (non-compensable), hypothermic zone (non-compensable), heat- and cold-resistant clothing (including ventilated pressure suits), combined thermal and other stresses (hypoxia, acceleration, etc.),

acclimatization, hibernation, and thermal models of humans. The 424 references are listed alphabetically by author under each category. Emphasis is placed on the literature since 1957.

Gillenwater, J. Y., E. D. Frohlect, and A. D. Killer. AD411470. Differential effects of heat on the splenic and renal vascular beds: vasoconstriction in the spleen and vasodilation in the kidney. Army Medical Research Lab., Report No. 579, Fort Knox, Ky. Temperature of the perfusate (blood) was increased for variable intervals of time from 32° to 42° C. (hyperthermic level) in the perfused kidney and spleen of the dog. The calculated resistance in the renal vascular bed decreased progressively as temperature was raised, whereas it increased progressively in the splenic vascular bed under identical circumstances.

Glaser, E.M. Simultaneous experimental acclimatization to heat and cold in man. J. Physiol. (London) 169:592-602 (Dec. 1963).

Glaser, E.M., F.R.Berridge, and K. M. Prior. Effect of heat and cold on the distribution of blood within the human body. Clin. Sci. 9:181-187 (1950).

Gold, J. A new theoretical heat stress index. Fed. Proc. 19:177 (1946).

Griminger, P., and H. S. Weiss. Coagulation of blood in temperature acclimatization. Nature (London) 197:1118 (16 Mar., 1963).

Gwozoz, B. The effect of high temperature on the human organism: The effect of humid heat on the oxygen content and carbon dioxide in the peripheral venous blood of man at rest. Acta Physiol. Pol. (Warsaw) 8(2):229-285 (1957). Oxygen and carbon dioxide content of the blood was measured in 59 men who had been exposed occupationally to high temperature (50°C. and 50 percent relative humidity) for 2 hours. There was an increase of oxygen content and a decrease of CO_2 in the blood. Increased velocity (fourfold) of the blood flow through extremities was the responsible factor.

Haddy, F. J., G. S. Camphill, and M. B. Virschir. Effects of changes in body temperature and inspired air humidity on lung edema and hemorrhage. Amer. J. Physiol. 158:429-432 (July-Sep. 1949). Under the conditions studied, hyperthermia favored the production of pulmonary edema, hemorrhage, and congestion in guinea pigs. The humidity of the inspired air was a factor of no great consequence in the production of preliminary lesions in these studies.

Hale, H. B., and E. W. Williams. Catecholamine excretion in heat-acclimatized men. AF School of Aerospace Med., N63-15847, Brooks AFB, Texas. Sympathoadrenal activity was appraised in 10 healthy men from late summer (when daily maximum temperature approached or exceeded 90°F) and into autumn, the study period amounting to 10 weeks. Two overnight urine samples per subject per week were analyzed for norephinephrine, epinephrine, creatinine, and urea. Evidence of high sympathoadrenal activity was obtained in summer, with reversal in autumn. Catecholamine excretion related either to weekly mean maximum temperatures, weekly mean solar radiation, or to both climatic factors and tended to vary

inversely with urea excretion. This variation may indicate interaction between catecholamines and thyroid hormone, the latter modifying metabolic actions of the former. The results suggest that catecholamines contribute to the regulation of blood distribution, a function of major importance in heat acclimatization.

Hale, H. B., and R. B. Mefferd. Metabolic effects of somatotropin in rats acclimated to adverse environments. J. Appl. Physiol. 16:243-246 (Mar. 1961).

Hale, H. B., and R. B. Mefferd. Effects of corticotropin on excretion responses of rats acclimated to various environments. AF School of Aviation Med., Report No. 59-81, Randolph AFB, Texas (August 1959).

Hale, H. B., et al. Influence of long-term exposure to adverse environments on organ weights and histology. Amer. J. Physiol. 196(3):520-524 (Mar. 1959).

Hale, H. B., and R. B. Mefferd. Factorial study of environmentally-induced metabolic changes in rats. Amer. J. Physiol. 194:469-475 (1958).

Hale, H. B., et al. Blood adrenocorticotrophic hormone and plasma corticosteroids in men exposed to adverse environmental condition. School of Aviation Med., AD 140-528, Randolph AFB, Texas Feb. 1957.

Hall, C. E., F. B. Engley, and T. Panos. The effect of exposure to high environmental temperatures on subsequent infection. School of Aviation Med., AD95146, Randolph AFB, Texas (Oct. 1955). The exposure of rats to environmental temperatures of 100°F. for an indefinite period resulted in an 87-percent mortality within two weeks. A marked decline was noted in the level of circulating eosinophils in rats exposed to this temperature for 24 hours. Heat of this degree applied for 24 and 48 hours, or 13 days did not sensitize the animals to a subsequent infection with Diplococcus pneumoniae. After 7 days of exposure, a positive sensitization was indicated. A temperature of 110°F., was fatal to rats after some 45 minutes (approximately) and all were dead within 2 hours. A 30-minute exposure caused a marked decline in circulating eosinophils, but did not sensitize the animals to a subsequent infection with D. pneumoniae. A temperature of 140°F. was fatal to rats within 45 minutes. A single

5-minute exposure at this temperature or three such exposures on successive days failed to sensitize subjects to subsequent infection. Thymic atrophy was a more reliable index of adrenal hyper-secretion when heat was used as a stressor.

Hall, J. F., and J. W. Polite. Physiological index of strain and body heat storage in hyperthermia. Appl. Physiol. 15(6):1027-1030 (Nov. 1960). The inter- and intraindividual variability of a modified Craig index of physiological strain, and the relationship between the index and body heat storage over an intensive thermal exposure range (38 to 71°C) were determined in male subjects wearing one clo of body insulation. Measurements were made of heart rate, sweat rate, rectal temperatures change rate, and initial and terminal skin temperatures. Individual variation from the main index of strain was considerable and apparently random at each thermal stress level. As the intensity of thermal stress was increased, data for body heat storage showed a progressive increase in standard deviation. A statistically significant correlation between strain index and body heat storage was observed.

Hardy, J. D. Physiology of temperature regulation. Physiol. Rev. 41:521-606 (1961).

Harrison, G. A. The adaptability of mice to high environmental temperatures. J. Exper. Biol. 35:892-901 (1958).

Hart, J. T., and L. Jansky. Thermogenesis due to exercise and cold in warm and cold-acclimatized rats. Canad. J. Biochem. 41:629-34 (Mar. 1963).

Hellmann, K., and J. S. Weiner. Antidiuretic substances in urine following exposure to high temperatures. Amer. J. Physiol. 6(3):194-198 (Sept. 1953). The effect of short exposure to high temperature on the output of antidiuretic substance in the urine of healthy young men has been studied. No antiduretic activity was found in the urine passed immediately prior to entering the hot room and rarely in the hot room itself. In nearly every case, urine passed after leaving the chamber, showed antidiuretic activity.

Hellon, R. F., R. M. Jones, R. K. Macpherson, and J. S. Weiner. Natural and artificial acclimatization to hot environment. J. Physiol. (132):559-576 (no date).

Hendler, E. Temperature effects on operator performance. In usual environments and human behavior: physiological and psychological problems of man in space, pp. 321-352. New York: Macmillan Co. 1963. The physical and physiological factors of temperature regulation are examined and their individual effects upon the performance of an operator are demonstrated by several examples.

Henschel, A., H. L. Taylor, and A. Keys. The persistence of heat acclimatization in man. Amer. J. Physiol. 140:321-325 (no date).

Hentschel, G. Relations of climatic factors to athletic performance. Deutsch Gesundh. 13(18):557-568 (1 May 1958).

Heroux, O. Climatic and temperature-induced changes in mammals. Rev. Canad. Biol. 20:55-68 (Apr. 1961).

Heroux, O. and E. Schoenbaum. Comparison between seasonal and thermal acclimation in white rats: III. Studies of the adrenal cortex. Canad. Jour. Biochem. 37:1255-1261 (Nov. 1959).

Heroux, O., and J. S. Campbell. Comparison between seasonal and thermal acclimation in white rats: IV. Morphological and pathological changes. Canad. Jour. Biochem. 37:1263-1269 (Nov. 1959).

Horvath, S. M., and W. B. Shelley. Acclimatization to extreme heat and its effect on the ability to work in less severe environments. Amer J. Physiol. 146:336-343 (no date).

Hunter, J. C. Effects of environmental hyperthermia on man and other mammals; a review. Military Med. 126(4):273-281 (Apr. 1961) A review is presented of studies on heat stress and effective temperature, physiological defenses against heat stress, acclimatization to heat, the effects of environmental hyperthermia, and countermeasures in the treatment of hyperthermia.

J

Johnson, G. E. Interrelationship of temperature on action of drugs. Fed. Proc. 22:745-749 (May-June 1963).

K

Kanter, G. S. Cause of hypophosphatemia in hyperthermia dogs. Amer. J. Physiol. 199(2):261-264 (Aug. 1960). Plasma inorganic phosphate fell from 3.9 to 1.6 mg. in eight unanesthetized dogs exposed to an air temperature of 48°C for two hours. The decline in inorganic phosphate was accompanied by a concomitant increase in whole blood (red cell) organic phosphorus. Hypophosphatemia was not observed in animals exposed to dehydration without hyperthermia or panting by heating at 40°C. or in curarized hyperthermic dog without panting. In five anesthetized, curarized, normothermic dogs artificially hyperventilated to simulate panting, pH was elevated and hypophosphatemia was observed. The increase in pH caused by panting is the major factor in the decrease of plasma inorganic phosphorus observed in dogs exposed to heat.

Kanter, G. S. Hypoglycemic effect of high environmental temperature on dogs. Amer. J. Phsiol. 188(3):443-446 (Mar. 1957). Two groups of dogs were subjected to a temperature of 120°F. at a relative humidity of 20 percent or below for 4 hours and blood glucose levels were determined. A third group was exposed twice, once for

3 hours at 120°F. and after a 2-hour cooling period, for another 3 hours. Blood glucose decreased 16 to 22 percent in dogs of the first two groups even with a corresponding dehydration of 6 percent of the body weight; controls had only a 4-percent decrease. The dogs re-exposed after a cooling period showed a fall in glucose despite a more severe dehydration. The drop in glucose noted in these experiments is evidently metabolic as no signs of glucosuria were found.

Kanter, G. S. Heat and hypoglycemia in dogs. Abstract in Fed. Proc. 15(1):104 (Mar. 1956). Exposure of 12 dogs to 120°F for four hours without access to water resulted in an average fall in whole blood glucose and plasma glucose of 19 and 13 percent respectively, in spite of an average final body-weight dehydration of 5.6 percent. In additional experiments, dogs were exposed to heat, and water balances were maintained by stomach tube administration, but hypoglycemia again resulted. The fall in glucose concentration may be associated with the increase in deep body temperature; because dehydration, a slight elevation in rectal temperature, and no decrease in glucose levels occur when dogs are exposed to the milder air temperature at 100°F.

Karvonen, M. J., M. Kinnenen, and R. Kaariainen. Flicker fusion frequency in sauna - bath. Int. F. Angew. Physiol. 16(2): 129-132 (1955). Flicker fusion frequency (FFF) was determined during exposure to high ambient temperatures in a Finnish Sauna-bath. FFF fell initially, but rose gradually to the pre-exposed level in 15 minutes. FFF was not dependent on body temperature and was not affected by rapid or gradual cooling. The initial decrease is attributed to the immediate reflex response of the cardiovascular system to a rapid rise in temperature.

Kaufman, W. C. Human tolerance limits for thermal environments of aerospace. Biomedical Lab., AD 405-633, Aerospace Medical Div. Wright-Patterson AFB. Ohio (no date). Experiments performed under thermal conditions simulating those of aerospace emergencies showed that man's tolerance to thermal stress is approximately twice that previously reported. Tolerance time was approximately doubled in long-term moderately severe thermal conditions, and in short intense periods of thermal stress associated with re-entry. Tolerance limits of the long term experiments were determined by general malaise. Symptoms were directly

related to the quantity of heat stored which was approximately 2.3 Kcal. per Kg of body weight in both long term and heat pulse experiments.

Kaufman, W. C. Changes in internal body temperatures during severe thermal stress. Presented at the forty-seventh Annual Meeting of the Federation of American Societies for Experimental Biology (no date). Internal body temperatures are of interest because of their purported involvement in temperature regulation. Rectal (T_R), endoesophageal (T_E), and tympanic (T_T) temperatures were recorded from 7 clothed (1 clo) subjects exposed to 400°F. thermal transients of 12 of 17 minutes (35 exposures), 160°F. ambient temperatures for 1 hour (6 exposures), and 40°F. ambient temperature for 1 hour (4 exposures). Mean control T_R was 37.5±0.16°C and T_T 36.9 ±0.08°C, but T_E did not vary significantly from T_T. During thermal strain, T_R and T_E converged: mean T_T was 1.2°C. higher and 2.3°C lower than T_R in the most severe transients and during cold exposure respectively. Change of T_T was most closely related to change in calculated mean body temperature and change of T_R least closely. In 35 thermal

transients, time of onset of facial sweating ranged from 2 to 7 minutes but occurred when T_T was 37.3± 0.08°C. However, in five exposures, facial sweating began while T_T was decreasing. Data indicate T_R and T_E represent a mean base temperature during thermal strain while T_T varies markedly with the thermal environment. Changes in hypothalamic temperature can only be nominal until their relation to T_T and T_R are more precisely known.

King, B. A. Temperature regulation and acclimatization: thought on heat illness: the clinical features of salt-depletion heat exhaustion. Proc. Mine. Med. Offices Assoc. 42:6-13 (May-Aug. 1963).

Kissen, A. L. Effect of hyperthermia on peripheral adaptations rates, J. Appl. Physiol. 18(3):600-602 (May 1963). Peripheral dark adaptation curves were obtained on five subjects at comfort 21.0°C. (comfort) and 65.6°C. temperatures alternately, using a modified Hecht-Schlaer adaptometer. In 24 heat experiments, subjects were exposed to 65.6°C ambient air temperature of 55.

minutes after which the heat was shut off. Chamber temperature declined but the subjects remained in a relatively constant hyperthermic condition during the subsequent 35-minute dark-adaptation test. The criterion for hyperthermia was the elevation and maintenance of the rectal temperature at least 0.56°C above corresponding control temperature. Curves obtained under hyperthermic conditions (with the exception of the initial and terminal values) differed with statistical significance from controls, indicating a facilitation of dark adaptation under the imposed thermal stress conditions.

Kuznets. E. D. On the problem of increasing the heat resistance of the body. Gig Sanit. 26:17-21 (May 1962).

L

Ladell, W.S.S., and R.J. Shephard. Aldosterone inhibition and acclimatization to heat. Proceedings of the Physiological Society, 3-4 November 1961. The possibility of inhibiting the action of aldosterone provides an opportunity of determining to what extent this hormone is essential for acclimatization to heat. Four unacclimatized subjects were exercised (mean metabolic cost approximately 100 Kcal./m^2/hr.) for 90 minutes in a hot wet climate (d. b. 38°C; w. b. 34°C; air movement, 17 meters per minute) each afternoon 5 days a week for 2 weeks. Rectal temperatures, pulse rates, and sweat losses were measured; sweat was collected every 20 minutes from an arm bag extending from the shoulder to below the hand.

Ladell, W.S.S. The influence of environment in arid regions on the biology of man: the physiological approach to climate. Rev. Research, UNESCO Arid Zone Research. VIII. Human and animal esology. Paris (no date).

Ladell, W.S.S. The effects of water and salt intake upon performance of men working in hot and humid environments. J. Physiol. (London) 127(1): 11-46 (Jan 1955). Under alternating work and rest conditions,

acclimatized men were exposed to environmental temperatures of 93 to 100°F. for up to 4 hours. Water loss, work performance, rectal temperature, pulse rate, and chloride loss were compared in subjects drinking no water or drinking 0.1-, 0.2-, or 0.5-percent saline during the experiment. The subjective effect of differences in water and salt intake was found to be more marked than the objective effect, and was manifested by sensations of fatigue. In a physical exercise, 18 failures (unable to continue) were recorded in 20 subjects given either salt and no water or a great excess of salt: in comparison there were 9 failures in 12 subjects who were given neither water nor salt; and 3 failures in 41 subjects given water with or without salt. Drinking water or not had no effect on the sweat rate, and only little effect on rectal temperature and heart rate. The administration of salt produced a relative decrease in rectal temperature and heart rate, and an increase in sweat rate when intake was lower than the chloride content of sweat. The unfavorable effects of abstention from water and salt could be predicted from changes in intracellular fluid volume and were perhaps also produced by alternations in adrenocortical activity and renal function.

Ladell, W.S.S. Assessment of group acclimatization to heat and humidity. J. Physiol. (London) (115):269-312 (no date).

Ladell, W.S.S. The decline in sweating with raised rectal temperature. J. Physiol. (London) 129:8 (no date).

Ladell, W.S.S. Changes in the chloride content of sweat with acclimatization. Biochem J. (39): XLVII (no date).

Lind, A.R. Practical assessment of intolerably hot conditions. Fed. Proc. 22:891 (May-June 1963). The WP formula may be used as a practical method for relating climates of similar tolerance times and for predicting actual tolerance times for men exposed to intolerable climates at several rates of energy expenditures. The actual values shown are average values and clearly some of the men will not tolerate the given conditions for this period. Provins, et al. states that 95 percent (at least) of the men will tolerate exposure for 75 percent of the average tolerance time and suggest this criterion to calculate "safe" exposure times.

Lind. A.R. Optimal exposure time for development of acclimatization to heat. Fed. Proc. 22:704-708 (May - June 1963).

Love, A.H.G., and R.G. Shanks. The relationship between the onset of sweating and vasodilatation in the forearm during body heating.

J. Physiol. (London) 162: (Jan. 1962). The blood flow through the forearm and the sweat production from an area of forearm have been measured before and during body heating. In the normal forearm, the increase in blood flow (in response to heating) may precede, coincide with, or follow the onset of sweating. Sweating always precedes or coincides with the onset of vasodilator nervous activity as inferred from a comparison of the changes in blood flow in the normal and the atropinized or nerve-blocked arm. These findings support the hypothesis that the cutaneous vasodilation in response to heating is secondary to activity of the sweat glands. Evidence does not exist for separate vascular vasodilator innervation.

M

Macpherson, R.K. Acclimatization status of temperate zone man. Nature (London) 182(4644): 1240-1241 (Nov. 1958).

Macpherson, R.K. Physiological responses to hot environments. Med. Res. Counc. Spec. Rep. (London) 298: (no date).

Malmijac. J., S. Cruk, and G. Neverrs. Role of cutaneous hyperthermia in the production of general disturbances due to high temperatures: mechanisms involved. Med. Aero. (Paris) 7(4): 441-447 (1952). Experiments were made on a flap of skin of an anesthetized dog exposed to high temperatures (60 to 70°C.) while the animal was breathing cold air. When the temperature of the flap reached 40 to 41°C., its blood supply was greatly increased, but decreased again at 42 to 43°C. The efferent blood of the hypothermic skin flap contained histamine and its protein balance was disturbed (increase of beta globulins). Hypothermia of the skin may be responsible for various (probably hepatic) reactions which affect the general circulation and may lead to circulatory collapse.

Mefferd, R.B., and H.B. Hale. Effects of abrupt temperature changes on excretion characteristics of rats acclimated to cold, neutral, or hot environments. Amer. J. Physiol. 195:726-734 (1958).

Merezhinskii, M.F., and L.S. Cherkasdva. Role of diets in the development of adaptation of the animal organism to changes in external temperature. Vop. Pitan 19:33-37 (May-June 1960).

N

Newman, M. T. Biological adaptation of man to his environment: Heat, cold, altitude and nutrition. An. N. Y. Acad. Sci. 91(3):617-633 (7 June 1961). The sensory survey of human adaptation to environmental extremes involves phenotypic alterations of morphological and physiological traits that are largely continuous variables. Heat and cold tolerance are discussed in terms of individual body size and proportions, skin surfaces area and pigmentation, subcultaneous fat, sweat glands and physiologic adjustments, e.g., vasoconstriction. Morphologic and physiologic adjustments to high altitudes may include large blood and lung volume and large red cell size and number. Nutritional adjustments are discussed in terms of hypocaloric and hyper-caloric intake. It seems clear, at least in general outline, that the nature as well as the degree of human adaptations to these facets of the environment unrelated in a direct sense to disease may indeed reflect upon disease situations.

Newman, R. W. Measurement of body fat in stress situation. Quartermaster Climatic Research Lab., AD 2579, Lawrence, Mass. The skin-fold technique described by Brozek and Keys (Brit. J. Nutrit.,

5:194, 1951) was used in two experiments; namely, prolonged heat exposure and the consumption of a survival ration. For the first experiment, 5 men were kept in an air-conditioned room at 75° F. for 3 weeks, at 120° F. during the day and 100° F. at night for 2 weeks, and then at 75° F. for 18 days. The men were placed on a rigid schedule of activity. The 10 men on the survival ration experiment were kept in an air-conditioned room at 80° F. for 13 days and were fed C-rations. For the next 10 days (in the same room and temperature), the subjects were given survival rations only and their activity was regulated. Data on body weight, body fat, caloric and water intake were recorded and analyzed for each experiment. The high fat values obtained in the heat study may have been caused by a peripheral vasodilatation. Body weight was influenced by the quantity of water consumed. In the absence of heat stress, the skin-fold method for estimating body fat gave excellent results. The weight loss of the subjects in both experiments was closely accounted for in terms of the adipose and protein tissue losses.

Robinson, S., E.S. Turrell, H.W. Belding, and S.M. Horvath. Rapid acclimatization to work in hot climates. Amer. J. Physiol. 140:168-176 (no date).

Robinson, S. Physiology of heat and clothing test methods. Newburgh, L.H. (ed), P.213. London: Saunders (no date).

Robinson, S., and S.D. Gerking. Thermal balance of men working in severe heat. Amer. J. Physiol. 149:476-488 (no date).

S

Saito, T. The prophylactic effect of head cooling on heat stroke: IV. The effect of combined treatment of head cooling and administration of aspartic salt on electrocardiogram. Tohoku Igaku F. 66:282-8 (Sep. 1963).

Salamone, L. On the reactions to ambient hyperthermia: VII. Modifications of serum iron. Boll. Soc. Ital. Biol. Sper. (Napoli) 29(8):1560-1561. An increased level of blood iron was determined in subjects exposed to heat (43 to 45°C) for two hours. Changes in tissue metabolism, blood volume erythrocytes, and splenic circulation (caused by hyperthermia) are among the factors responsible for this phenomenon.

Shiratori, T. The prophylactic effect of head-cooling on coal miner's cramps. The electroencephalographic observation on rabbits during head cooling under the hot and humid environment. Tohoku Igaku F. 66:266-271 (Sep. 1962).

Silverman, A.J., S.I. Cohen, G.D. Fuidema, and C.S. Lazar. Prediction of physiological stress tolerance from projective tests: "The

focused thematic test." J. Projective Techniques 21(2):189-193 (June 1957). A thematic-type test focused on the area of direction of comfort in handling aggressive stimuli and situations was used to predict the g-tolerance of three groups of subjects. Adrenaline/noradrenaline rations, anger-in/anger-out directions of aggression, and blood pressure patterns were integrated on a basis for predicting g-stress tolerance from projective tests. It was predicted that high g-stress tolerance would relate to outward aggression, while low tolerance would relate to aggression toward the self. G-stress tolerance was determined in a human centrifuge and direction of aggression was elicited with a TAT-like story test. In a preliminary sample, two psychologists independently made correct placements of 12 out of 13 subjects that were selected from the extremes of the distribution of g tolerances, from the stories told to the Focused Projective Tests. High g-stress tolerance subjects tell of heroes who take an obdurate, aggressive, and impulsive role. Low g-stress tolerance subjects tell of heroes who are dependent, inhibited, and controlled by others. Two further validation studies in which the judges predicted the high/low g tolerances from the stories of the Focused Thematic Tests were significant at the 0.01 level for the first group, an Air Force population, and significant at the 0.05 level for the second group, a student population.

Stickney, J.C., D.W. Morthup, and E.J. Van Leire. Hyperthermia and intestinal motility in rats. Fed. Proc. 15(1[I]):180(Mar. 1956). In two groups of experimental rats, body temperature was elevated by keeping the rats in the field of a diathermy machine. The elevation was produced during 5 minutes before gastric intubation and was maintained until killing for removal of the small intestine. In the first experimental group the preintubation body temperature averaged 49.1 C or 1.9°C above that of the control group. No statistically significant differences were seen in the 9 pairs of control and experimental rats in which 61 and 53 percent of the small intestine was transversed respectively. In the second experimental group, the body temperature averaged 41.8°C or 3.7°C above that of the control group. The percentage of the intestine transversed in the 8 control rats was 51 as compared with 24 in 9 experimental rats. The difference of 27 percent is statistically significant at less than the 0.1 percent level and is evidence that severe elevations of body temperature depressed motility in the rat.

T

Taylor, C. L. Human tolerances for temperature extremes. In White, C.S., et al. (ed.). Physics and medicine of the upper atmosphere: a study of the aerospace, pp. 548-561. Albuquerque: University of New Mexico Press, 1952. Pressurization and air conditioning of aircraft have limited the problem of human tolerance of extreme temperatures to incidences of cabin failure. However, in ultrasonic flight, air friction of the fuselage produces surface temperatures which surpass human tolerances. Air Force waist gunners wearing heavy clothing with supplementary electrical heating have withstood an environmental air temperature of -40°C. A pilot provided with heavy clothing is able to withstand temperatures up to -5°C. in his normal resting position, and up to -40°C. during work equivalent to walking at a speed of 2.5 m.p.h. The basic principles involved in body heat, extreme heat, cold exposures, and the effects of exercise are discussed.

Terranova, S. On the reactions to ambient hyperthermia. VI. Electrocardiographic and ballistocardiographic findings. Boll. Soc. Ital. Biol. Sper. (Napoli) 29(8): 1558-1559 (July-Aug. 1953). Electroencephalography in subjects exposed to heat (43 to 45°C.) for two hours

demonstrated a moderate and inconsistent increase in cardiac frequency. T-wave modifications, related to potassemia, were also noted. Ballistocardiographic tracings in the same subjects revealed a constant reduction in the amplitude of systolic oscillations (H, I, J, and K), indicating reduced systolic activity caused by hyperthermia.

W

Weiner, J.S., and R.E. Van Heyningen. Salt losses of men working in hot environments. Brit. J. Indus. Med. (London) 9(1):56-64 (Jan. 1952). The sweat and urinary loss of chloride has been studied in individuals working in hot conditions for short periods. Acclimatization to heat is only accompanied by a decrease in the chloride concentration of general body sweat if a negative chloride balance is induced by restriction of the chloride intake. Sweating for short periods (two hours) in unacclimatized subjects brings about a compensatory reduction of urinary chloride manifested after the subjects leave the hot room. This reduction is so great that the total loss of chloride may be less on days in which sweating occurs than in the control days. Attention is drawn to the limitations to the use of sweat collected in arm bags as a method of assessing the body salt balance. These findings increase the desirability of supplementing the salt intake in the diet.

Welch, B.E., E.R. Buskirk, and P.F. Iampietro. The relation of climate and temperature to food and water intake in man. Metabolism 7(2):141-148 (Mar. 1958).

William, C.G. et al. Circulatory and metabolic reactions to work in heat. J. Appl. Physiol. 17:625 (1962).

Wissler, E.H. A mathematical model of the human thermal system. AD 294 127. The latest in a series of mathematical models for the human thermal system is described. In preparing this model, finite-difference techniques were used to solve the heat conduction equation. Since numerical techniques were used, many more factors were included in this model than in the previous ones. The body was divided into the following fifteen geometric regions: head, thorax, abdomen, and proximal, medial, and distal segments of the arms and legs; axial gradients in a given segment were neglected. In each segment, the large arteries and veins were approximated by arterial and venous pools which were distributed radially throughout the segment. Accumulation of heat in the blood of the large arteries and veins and heat transfer from the large arteries and veins to the surrounding tissue were taken into account. The venous streams were collected together at the heart before flowing into the capillaries of the lung. Each of the segments was subdivided into fifteen radical sections,

thereby allowing considerable freedom in the assignment of physical properties such as thermal conductivity and rate of blood flow to the capillaries.

Wolkin, J., J.I. Goodman, and W.E. Kelley. Failure of the sweat mechanism in the desert: thermogenic anhidrosis. J.A.M.A. (124):478-482.

Wood, J.E., and D.E. Bass, Responses of the veins and arterioles of the forearm to walking during acclimatization to heat in mass. J. Clin. Invest. 39(6):825-833 (1960). Plethysmographic studies of venous tone and blood flow of the forearm were carried out to determine whether or not the increasing adequacy of general circulation with acclimatization to heat was associated with alterations of peripheral circulation. Subjects were acclimatized to heat by walking for 30 minutes 4 times a day on a tread-mill at 3.5 m.p.h. with a 5-percent grade. Two studies of 4 subjects each were carried out with 2-and 1-control days respectively (77°F.), and in 9 and 6 heat days (120°F.) respectively. The veins of the forearm constricted in response to walking in both environments. This venoconstriction on the third and fourth day in the hot environment was significantly greater than that of

other days in the heat or in the control environments. Blood flow of the forearm during walking was much greater in the hot environment than in the cool environment but relatively less on the third-and fourth-day in the hot environment than on other days in the hot environment. Peripheral vascular responses to walking in the heat were most intense on the third and fourth day in the hot environment when the men showed the greatest subjective improvement with walking in the heat. However, these effects did not persist, suggesting that other factors also contributed to the improved circulatory responses with acclimatization to heat.

Wyndham, C.H., N.B. Strydom, H.M. Cooke, and J.S. Maritz. The temperature responses of men after two methods of acclimatization. Int. Z. Angew. Physiol. 18:112-122 (1960).

Wyndham, C.H. Effect of acclimatization on circulatory responses to high environmental temperatures. J. Appl. Physiol. (4):383-395 (no date).

Wyndham, C.H., et al. A new method of acclimatization to heat. South African J. Med. Sci. (Johannesburg) 19(4):171 (Dec. 1954). A new method of acclimatization described by N.B. Strydom (Item No. 3516)

was tested in a field trial, using 110 laborers. The men were exposed to the same rate of work as fully acclimatized men but worked in mild heat (86.5°F.) for 6 days. This period was followed by 6 days of work (shoveling rock in a mine) in severe heat (91.5°F.) Rectal temperatures were measured at 7, 8, 11 and 1 o'clock each working day. The mean vital temperature fell from 101.0°F. on the first day to 100.0°F. on the twelfth day. Moreover, a partial state of acclimatization was produced during the first week as indicated by the fact that the mean temperature was lower (100.8°F.) on the first day in the hot stope than on the first day in the cool stope (101.0°F). Only on the first and second days did the mean body temperature of 40 complete novices significantly exceed that of 70 men returning for the second or third time. There were 23 cases of subjects with occasional rectal temperatures in excess of 103.0°F. Most of these cases could be attributed to illness; some occurred during the first two critical days of adaptation or in association with excessively hard work. This method of acclimatization is effective in producing adequate physiological adjustment and a satisfactory rate of work.

AUTHOR UNKNOWN

Human tolerance for short exposures to heat. 6570th Aerospace Medical Research Lab., AD 410 729, Aerospace Medical Div., Wright-Patterson AFB, Ohio. The development of very high speed fighter aircraft creates the problem of excessive cockpit temperature, particularly in fast sweeps at low altitude. The heat comes from three sources, namely, solar radiation transmitted through the Pleugler bubble canopy, friction of the air passing over the surface of the fuselage, and the ram pressure heat. For example, the last named phenomenon may cause a temperature rise above OAT of 29, 45, and 64°F. at speeds of 400, 500 and 600 m.p.h. respectively. If another 10 to 15°F. effective temperature is added by solar radiation, cabin temperature in excess of 150°F. may be expected even when ambient temperature is between 90 and 100°F. Since the duration of exposure to these high temperatures is expected to be short (15 to 30 minutes at a maximum), steady states of human heat balance are not required. The biophysical problem is to determine points on a duration-intensity curve which are tolerable for Air Force personnel. In selecting these points, it must be assumed that pilots are not heat acclimatized and that they represent a range of constitutional and fitness types.

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13. ABSTRACT

This volume is a continuation of the literature survey conducted to evaluate acclimatization versus tolerance to stress and contains a compilation of titles and abstracts dealing with altitude acclimatization as related to acute hypoxia, decompression, hypercapnia and hyperthermia. The bibliography is arranged alphabetically by authors' names.

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Hypoxia, acute						
Decompression						
Hypercapnia						
Hyperthermia						
Acclimatization (literature survey)						
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